#17

IN THE UNITED STATES PATENT AND TRADE MARK OFFICE

In re application of
Ohkawa, et al.
Serial No. 08/812,168
Filed March 6, 1997
For : Trycyclic compounds, their production and use

D E C L A R A T I O N

I, Takuya Abe, technical translator, declare that I am a citizen of Japan, residing at 2-2-3, Satsukigaoka, Ikeda, Osaka, Japan: that I am competent to make English translations and have had considerable experience in that work; that the attached are true translations into the English language of the Japanese Patent Application No. 051491/1996.

I, the undersigned, declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are publishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 22nd day of December, 1998

Takuya Abe

Takuya Abe

PATENT OFFICE
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This is to certify that the annexed is a true copy of the following application as filed with this Office.

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Application Number : No. 051491/1996
Applicant : Takeda Chemical Industries, Ltd.

April 25, 1997

Commissioner,
Patent Office Hisamitsu Arai

Certificate No. Hei09-3029830

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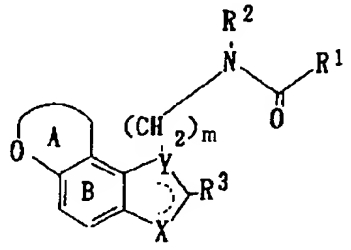
[NAME OF DOCUMENT] SPECIFICATION

[TITLE OF THE INVENTION] TRICYCLIC COMPOUNDS, THEIR PRODUCTION AND COMPOSITION

[SCOPE OF DEMAND FOR PATENT]

[Claim 1] A compound of the formula:

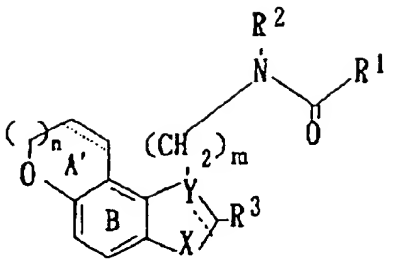


(I)

wherein R^1 represents an optionally substituted hydrocarbon group, an optionally substituted amino group or an optionally substituted heterocyclic group;
R^2 represents a hydrogen atom or an optionally substituted hydrocarbon group;
R^3 represents a hydrogen atom, an optionally substituted hydrocarbon group, or an optionally substituted heterocyclic group;
X represents CHR^4, NR^4, O or S (in which R^4 represents a hydrogen atom or an optionally substituted hydrocarbon group);
Y represents C, CH or N, provided that when X is CH_2, Y is C or CH;

$\overline{\text{-----}}$ represents a single bond or a double bond;
ring A represents an optionally substituted, 5- to 7-membered oxygen-containing heterocyclic ring;
ring B represents an optionally substituted benzene ring; and
m represents an integer of 1 to 4,
or a salt thereof.

[Claim 2] The compound as claimed in claim 1 which is a compound of the formula:



(II)

wherein ring A' represents an optionally substituted, oxygen-containing heterocyclic ring;
n represents an integer of 0 to 2;

----- and ..... are the same or different and each represents a single bond or a double bond;
and the other symbols are as defined in claim 1.

[Claim 3] The compound as claimed in claim 1 or 2, wherein R^1 is

(i) an optionally substituted C_{1-6} alkyl group,
(ii) an optionally substituted C_{3-6} cycloalkyl group,
(iii) an optionally substituted C_{2-6} alkenyl group,
(iv) an optionally substituted C_{6-14} aryl group,
(v) an optionally substituted mono- or di-C_{1-6} alkylamino group,
(vi) an optionally substituted C_{6-14} arylamino group, or
(vii) an optionally substituted 5- or 6-membered nitrogen-containing heterocyclic group.

[Claim 4] The compound as claimed in claim 3, wherein R^1 is an optionally halogenated C_{1-6} alkyl group.

[Claim 5] The compound as claimed in claim 1 or 2, wherein R^2 is a hydrogen atom or an optionally substituted C_{1-6} alkyl group.

[Claim 6] The compound as claimed in claim 1 or 2, wherein R^3 is a hydrogen atom or an optionally substituted hydrocarbon group.

[Claim 7] The compound as claimed in claim 1 or 2,

wherein R^4 is a hydrogen atom or an optionally substituted C_{1-6} alkyl group.

[Claim 8] The compound as claimed in claim 1, wherein X is CHR^4 (in which R^4 is as defined in claim 1).

[Claim 9] The compound as claimed in claim 1, wherein X is NR^4 (in which R^4 is as defined in claim 1).

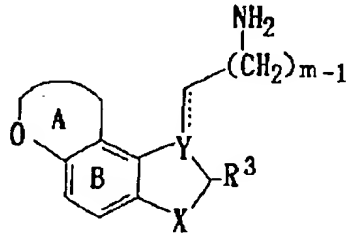
[Claim 10] The compound as claimed in claim 1 or 2, wherein Y is C or CH.

[Claim 11] The compound as claimed in claim 1 or 2, wherein m is 2.

[Claim 12] The compound as claimed in claim 1, wherein ring A is unsubstituted.

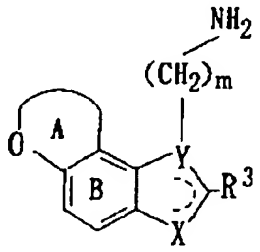
[Claim 13] The compound as claimed in claim 2, wherein n is 0 or 1.

[Claim 14] A process for producing a compound as claimed in claim 1, which comprises reacting (i) a compound of the formula:



wherein all symbols are as defined in claim 1, or a salt thereof, or

(ii) a compound of the formula:

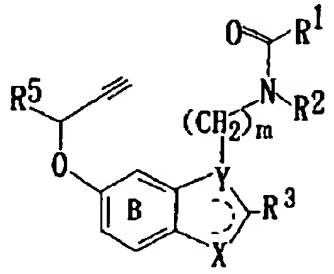


wherein all symbols are as defined in claim 1, or a salt thereof, with a compound of the formula:

R^1COOH

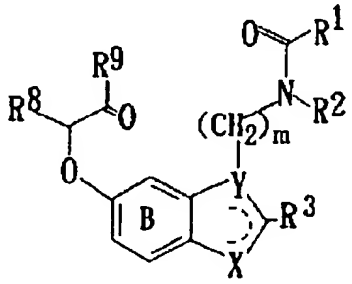
wherein R^1 is as defined in claim 1, or a salt thereof or a reactive derivative thereof, if necessary, subjecting the resultant compound to reduction.

[Claim 15] A process for producing a compound as claimed in claim 2, which comprises subjecting (i) a compound of the formula:



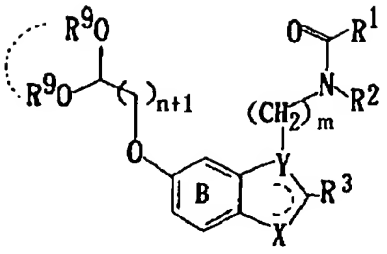
wherein R^5 represents a hydrogen atom, a halogen atom, an optionally substituted hydrocarbon group, an optionally substituted alkoxy group, a hydroxyl group, a nitro group, a cyano group or an optionally substituted amino group; and the other symbols are as defined in claim 2, or a salt thereof,

(ii) a compound of the formula:



wherein R^8 represents a hydrogen atom, a halogen atom, an optionally substituted hydrocarbon group, an optionally substituted alkoxy group, a hydroxyl group, a nitro group, a cyano group or an optionally substituted amino group; R^9 represents a hydrocarbon group; and the other symbols are as defined above, or a salt thereof, or

(iii) a compound of the formula:



wherein R^9 represents a hydrocarbon group, or two R^9 groups may be bonded to each other to form a ring;

n is as defined in claim 2; and

the other symbols are as defined above, or a salt thereof to cyclization, if necessary subjecting the resultant compound to reduction.

[Claim 16] A pharmaceutical composition which comprises a compound as claimed in claim 1.

[Claim 17] The pharmaceutical composition as claimed in claim 16, which has a binding affinity for melatonin receptor.

[Claim 18] The pharmaceutical composition as claimed in claim 17, which is a regulating agent of circadian rhythm.

[Claim 19] The pharmaceutical composition as claimed in claim 17, which is a regulating agent of sleep-awake rhythm.

[Claim 20] The pharmaceutical composition as claimed in claim 17, which is a regulating agent of time zone change syndrome.

[Claim 21] The pharmaceutical composition as claimed in claim 17, which is a therapeutic agent of sleep disorders.

[DETAILED DESCRIPTION OF THE INVENTION]

[0001]

[FIELD OF THE INVENTION]

The present invention relates to a tricyclic compound with excellent binding affinity for melatonin receptor, a process for producing and a preparation

comprising it.

[0002]

[BACKGROUND OF THE INVENTION]

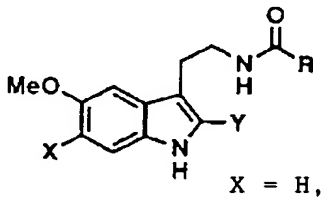
Melatonin (N-acetyl-5-methoxytryptamine), which is a hormone synthesized and secreted principally in the pineal gland, increases in dark circumstances and decreases in light circumstances. Melatonin exerts suppressively on pigment cells and the female gonads, and acts as a synchronous factor of biological clock while taking part in transmittance of photoperiodic code. Therefore, melatonin is expected to be used for the therapy of diseases related with melatonin activity, such as reproduction and endocrinic disorders, sleep-awake rhythm disorders, jet-lag syndrome and various disorders related to aging, etc.

Recently, it has been reported that the production of melatonin melatonin could reset the body's aging clock (see Ann. N. Y. Acad. Sci., Vol. 719, pp. 456-460 (1994)). As previously reported, however, melatonin is easily metabolized by metabolic enzymes *in vivo* (see Clinical Examinations, Vol. 38, No. 11, pp. 282-284 (1994)). Therefore, it cannot be said that melatonin is suitable as a pharmaceutical substance.

[0003]

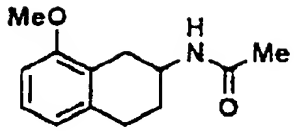
Various melatonin agonists and antagonists such as those mentioned below are known.

(1) EP-A-578620 discloses compounds of:

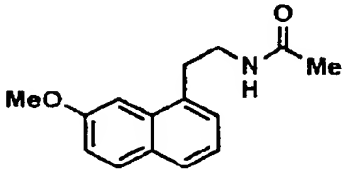


X = H, Y = Br, R = Me
X = H, Y = I, R = Me
X = Cl, Y = H, R = Me
X = H, Y = CH_3, R = cyclopropyl

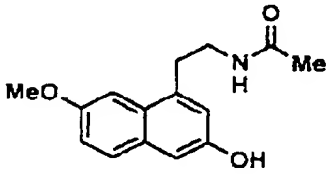
(2) US-411675 discloses a compound of:



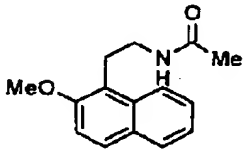
(3) EP-A-447285 discloses a compound of:



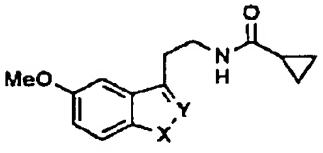
(4) FR-014630 discloses a compound of:

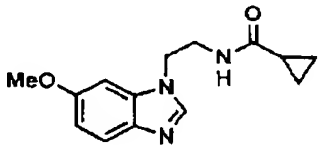


(5) EP-A-591057 discloses a compound of:



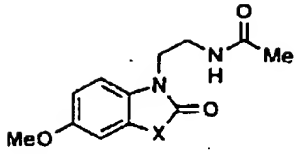
(6) EP-A-527687 discloses compounds of:



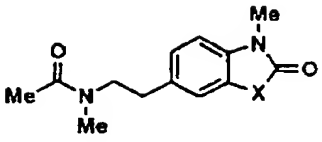


X = S, O, Y = CH
X = O, NH, Y = N

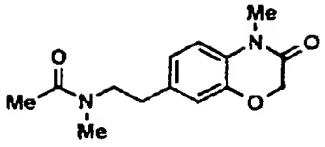
(7) EP-A-506539 discloses compounds of:



X = O, S



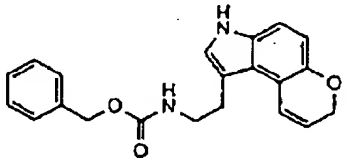
X = O, S

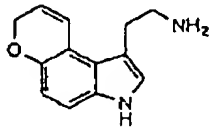


These are known as melatonin agonists or antagonists.

Tricyclic or more poly-cyclic compounds with a cyclic ether moiety, such as those mentioned below, are known.

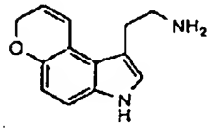
(1) Compounds of:





are disclosed in Tetrahedron Lett., Vol. 36, p. 7019 (1995).

(2) Compounds of:



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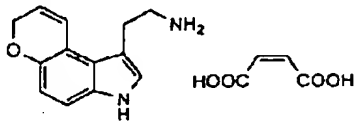

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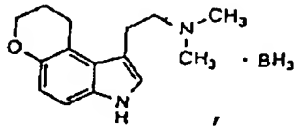

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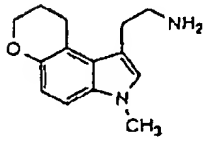

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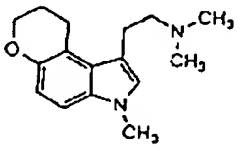

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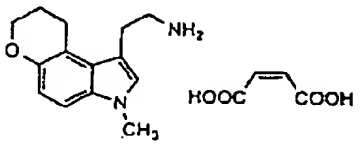
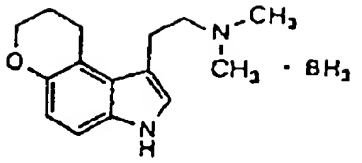
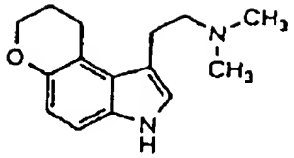


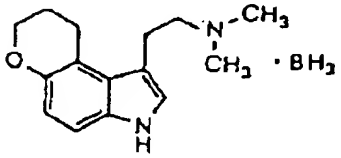
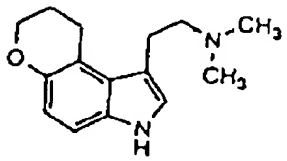
are in J. Med. Chem., Vol. 35, p. 3625 (1992).

(3) Compounds of:

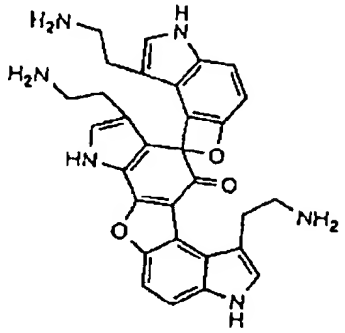
are in Tetrahedron, Vol. 48, p. 1039 (1992).

(4) Compounds of:

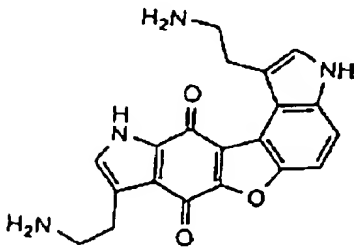
are in Tetrahedron Lett., Vol. 32, p. 3345 (1991).

(5) A compound of:



is in Bioorg. Chem., Vol. 18, p. 291 (1990).

(6) A compound of:

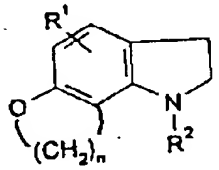


is in J. Electroanal. Chem. Interfacial Electrochem., Vol. 278, p. 249 (1990).

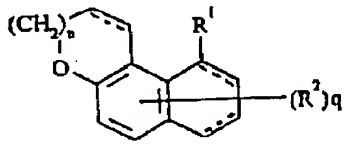
However, there is no report referring to the relationship between these compounds and melatonin receptors.

[0004]

As tricyclic compounds with an affinity for melatonin receptor, known are compounds of:



wherein R^1 represents a hydrogen atom, a halogen atom or a C_{1-6} alkyl group;
R^2 represents $-CR^3R^4(CH_2)_pNR^5COR^6$ (in which R^3, R^4 and R^5 are the same or different and each represents a hydrogen atom or a C_{1-6} alkyl group, and R^6 represents a C_{1-6} alkyl group or a C_{3-7} cycloalkyl group);
n represents an integer of 2 to 4, and p represents an integer of from 1 to 4 (WO-A-9517405); and
compounds of:



wherein R^1 represents $-CR^3R^4(CH_2)_pNR^5COR^6$ (in which R^3, R^4 and R^5 are the same or different and each represents a hydrogen atom or a C_{1-6} alkyl group, and R^6 represents a C_{1-6} alkyl group or a C_{3-7} cycloalkyl group);
R^2 represents a hydrogen atom, a halogen atom, a C_{1-6} alkyl group, OR^7 or CO_2R^7 (in which R^7 represents a hydrogen atom or a C_{1-6} alkyl group), provided that when q is 2, each of R^2 are the same or different and each

represents a hydrogen atom, a halogen atom, a C_{1-6} alkyl group, OR^7 or CO_2R^7;
n represents an integer of 0 to 2, p represents an integer of 1 to 4, and q represents 1 or 2 (WO-A-9529173).

[0005]

[PROBLEMS THE INVENTION SOLVES]

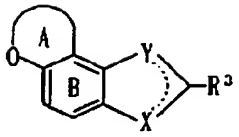
Melatonin agonists having structures different from that of melatonin and having an excellent binding affinity for melatonin receptors, excellent intracerebral mobility and excellent metabolical stability are expected to be more effective as a pharmaceutical remedy than melatonin.

At present, no compounds are known which are fully satisfactory with respect to their activity on melatonin receptors, and to their metabolical stability and the intracerebral mobility. Therefore, it is earnestly desired to develop compounds which are different from the above-mentioned known compounds in terms of their chemical structure, which have excellent agonistic or antagonistic activity towards melatonin receptors and which are therefore fully satisfactory for use in medicines such as pharmaceutical preparations.

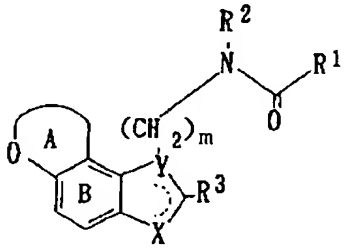
[0006]

[MEASURES FOR SOLVING THE PROBLEMS]

The present inventors have assiduously studied and, as a result, have succeeded in the production of novel compounds which is characterized in having a R^1-CO-amino- C_{1-4} alkylene group (in which R^1 is of the same meanings as defined hereinafter) at Y of the basic skeleton moiety of the formula:



wherein all symbols are as defined mentioned above and represented by the formula:



(I)

wherein R^1 represents an optionally substituted hydrocarbon group, an optionally substituted amino group or an optionally substituted heterocyclic group;
R^2 represents a hydrogen atom, or an optionally substituted hydrocarbon group;
R^3 represents a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted heterocyclic group;
X represents CHR^4, NR^4, O or S (in which R^4 represents a hydrogen atom or an optionally substituted hydrocarbon group);
Y represents C, CH or N, provided that when X is CH_2, Y is C or CH;

----- represents a single bond or a double bond;
ring A represents an optionally-substituted, 5- to 7-membered oxygen-containing heterocyclic ring;
ring B represents an optionally substituted benzene ring; and
m represents an integer of 1 to 4, or a salt thereof, and found that the novel compound (I) or a salt thereof have high stability and a good affinity for melatonin

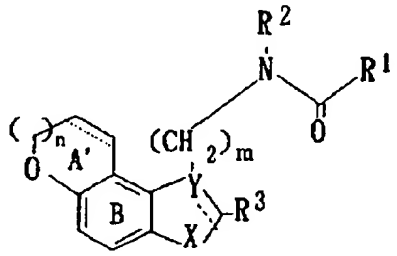
receptors as melatonin agonists or antagonists and are therefore sufficiently satisfactory for use in medicines such as pharmaceutical preparations. On the basis of these findings, the prevent inventors have completed the present invention.

[0007]

Specifically, the present invention provides;

(1) the compound (I) or a salt thereof,

(2) the compound of the foregoing (1), which are represented by a formula:



(II)

wherein ring A' represents an optionally-substituted, oxygen-containing heterocyclic ring;
n represents an integer of 0 to 2;
----- and ····· are the same or different and each represents a single bond or a double bond;
and the other symbols are as defined in (1),

(3) the compound of the foregoing (1) or (2), wherein R^1 is (i) an optionally substituted C_{1-6} alkyl group, (ii) an optionally substituted C_{3-6} cycloalkyl group, (iii) an optionally substituted C_{2-6} alkenyl group, (iv) an optionally substituted C_{6-14} aryl group, (v) an optionally substituted mono- or di-C_{1-6} alkylamino group, (vi) an optionally substituted C_{6-14} arylamino group, or (vii) an optionally substituted, 5-membered or 6-membered, nitrogen-containing heterocyclic group,

(4) the compound of the foregoing (3), wherein R^1

is an optionally halogenated C_{1-6} alkyl group,

(5) the compound of the foregoing (1) or (2), wherein R^2 is a hydrogen atom or an optionally substituted C_{1-6} alkyl group,

(6) the compound of the foregoing (1) or (2), wherein R^3 is a hydrogen atom or an optionally substituted hydrocarbon group,

(7) the compound of the foregoing (1) or (2), wherein R^4 is a hydrogen atom or an optionally substituted C_{1-6} alkyl group,

(8) the compound of the foregoing (1), wherein X is CHR^4 (in which R^4 is as defined in (1)),

(9) the compound of the foregoing (1), wherein X is NR^4 (in which R^4 is as defined in (1)),

(10) the compound of the foregoing (1) or (2), wherein Y is C or CH,

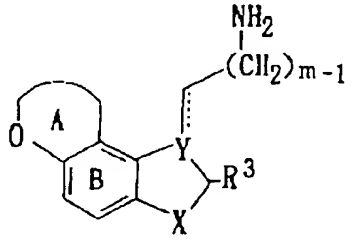
(11) the compound of the foregoing (1) or (2), wherein m is 2,

(12) the compound of the foregoing (1), wherein ring A is unsubstituted,

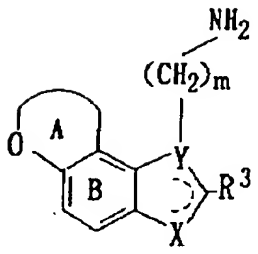
(13) the compound of the foregoing (2), wherein n is 0 or 1,

[0008]

(14) a process for producing a compound of the foregoing (1), which comprises reacting (i) a compound of the formula:



where the symbols are as defined in (1), or its salt, or (ii) a compound of a formula:

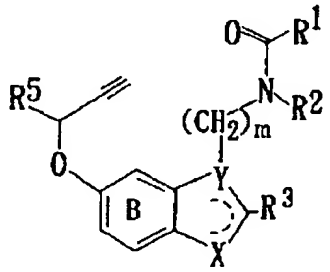


where the symbols are as defined in (1),
or its salt, with a compound of the formula:

R^1COOH

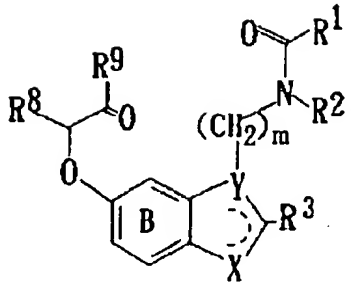
where R^1 is as defined in (1),
or its salt or reactive derivative, if necessary,
subjecting the resultant compound to reduction,

(15) a process for producing a compound of the foregoing (2), which comprises subjecting (i) a compound of a formula:



where R^5 represents a hydrogen atom, a halogen atom, an optionally substituted hydrocarbon group, an optionally substituted alkoxy group, a hydroxyl group, a nitro group, a cyano group or an optionally substituted amino group; and

the other symbols are as defined in (2),
or its salt, or (ii) a compound of a formula:

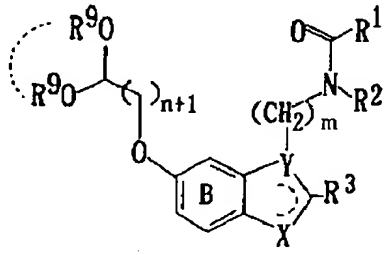


where R^8 represents a hydrogen atom, a halogen atom, an optionally substituted hydrocarbon group, an optionally substituted alkoxy group, a hydroxyl group, a nitro group, a cyano group or an optionally substituted amino group;

R^9 represents a hydrocarbon group; and

the other symbols are as defined above,

or its salt, or (iii) a compound of a formula:



where R^9 represents a hydrocarbon group, or two R^9 groups may be bonded to each other to form a ring;

n is as defined in (2); and

the other symbols are as defined above,

or its salt to cyclization, if necessary, subjecting the resultant compound to reduction,

(16) a pharmaceutical composition comprising the compound of the foregoing (1),

(17) the pharmaceutical composition of the foregoing (16), which has an affinity for melatonin receptor,

(18) the pharmaceutical composition of the

foregoing (17), which is a regulating agent of circadian rhythm,

(19) the pharmaceutical composition of the foregoing (17), which is a regulating agent of sleep-awake rhythm,

(20) the pharmaceutical composition of the foregoing (17), which is a regulating agent of time zone change syndrome,

(21) the pharmaceutical composition of the foregoing (17), which is a therapeutic agent of sleep disorders.

[0009]

The "hydrocarbon group" in the terminology "optionally substituted hydrocarbon group" as referred to herein includes, for example, an aliphatic hydrocarbon group, a mono-cyclic saturated hydrocarbon group, an aromatic hydrocarbon group, etc., and this preferably has from 1 to 16 carbon atoms. Concretely, this includes, for example, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, an aryl group, etc.

The "alkyl group" is, for example, preferably a lower alkyl group and generally includes C_{1-6} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.

The "alkenyl group" is, for example, preferably a lower alkenyl group and generally includes C_{2-6} alkenyl groups such as vinyl, 1-propenyl, allyl, isopropenyl, butenyl, isobutenyl, etc.

The "alkynyl group" is, for example, preferably a lower alkynyl group and generally includes C_{2-6} alkynyl groups such as ethynyl, propargyl, 1-propynyl, etc.

The "cycloalkyl group" is, for example, preferably a lower cycloalkyl group and generally includes C_{3-6}

cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

The "aryl group" is preferably a C_{6-14} aryl group, including, for example, phenyl, xylyl, 1-naphthyl, 2-naphthyl, biphenylyl, 2-indenyl, 2-anthryl, etc. Of these, phenyl is generally used.

[0010]

The substituents for the "hydrocarbon group" of the "optionally substituted hydrocarbon group" include, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), a nitro group, a cyano group, a hydroxyl group, an optionally halogenated lower alkyl group (e.g., an optionally halogenated C_{1-6} alkyl group, such as methyl, chloromethyl, difluoromethyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, propyl, 3,3,3-trifluoropropyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, 4,4,4-trifluorobutyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl, hexyl, 6,6,6-trifluorohexyl, etc.), a lower alkoxy group (e.g., a C_{1-6} alkoxy group, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentyloxy, hexyloxy, etc.), an amino group, a mono-lower alkylamino group (e.g., a mono-C_{1-6} alkylamino group, such as methylamino, ethylamino, etc.), a di-lower alkylamino group (e.g., a di-C_{1-6} lower alkylamino group, such as dimethylamino, diethylamino, etc.), a carboxyl group, a lower alkyl-carbonyl group (e.g., a C_{1-6} alkyl-carbonyl group, such as acetyl, propionyl, etc.), a lower alkoxy-carbonyl group (e.g., a C_{1-6} alkoxy-carbonyl group, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, etc.), a carbamoyl group, a mono-lower alkylcarbamoyl group (e.g., a mono-C_{1-6} alkylcarbamoyl group, such as methylcarbamoyl,

ethylcarbamoyl, etc.), a di-lower alkylcarbamoyl group (e.g., a di-C_{1-6} alkylcarbamoyl group, such as dimethylcarbamoyl, diethylcarbamoyl, etc.), an arylcarbamoyl group (e.g., a C_{6-10} aryl-carbamoyl group, such as phenylcarbamoyl, naphthylcarbamoyl, etc.), an aryl group (e.g., a C_{6-10} aryl group, such as phenyl, naphthyl, etc.), an aryloxy group (e.g., a C_{6-10} aryloxy group, such as phenyloxy, naphthyloxy, etc.), an optionally halogenated lower alkylcarbonylamino group (e.g., an optionally halogenated C_{1-6} alkyl carbonylamino group, such as acetylamino, trifluoroacetylamino, etc.), etc. The "hydrocarbon group" of the "optionally substituted hydrocarbon group" may have 1 to 5, preferably 1 to 3 substituents selected from, for example, those mentioned above, at any substitutable positions in the group. In the case in which the group has two or more substituents, the plural substituents may be the same or different.
[0011]

The term "heterocyclic group" in the terminology "optionally substituted heterocyclic group" as referred to herein refers to, for example, 5-membered to 14-membered (preferably, 5-membered to 10-membered), mono-cyclic to tri-cyclic (preferably mono-cyclic or di-cyclic) heterocyclic groups each having 1 or 2 kinds, 1 to 4 (preferably 1 to 3) hetero atoms selected from nitrogen, oxygen and sulfur, in addition to carbon atoms, etc. Concretely, it includes, for example, a 5-membered heterocyclic group having 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen, in addition to carbon atoms, such as 2- or 3-thienyl, 2- or 3-furyl, 1-, 2- or 3-pyrrolyl, 1-, 2- or 3-pyrrolidinyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 3-, 4- or 5-

pyrazolyl, 2-, 3- or 4-pyrazolidinyl, 2-, 4-, or 5-imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1H- or 2H-tetrazolyl, etc.; a 6-membered heterocyclic group having 1 to 4 hetero atoms selected from, for example, oxygen, sulfur and nitrogen atoms, in addition to carbon atoms, such as 2-, 3- or 4-pyridyl, N-oxido-2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, N-oxido-2-, 4- or 5-pyrimidinyl, thiomorpholinyl, morpholinyl, piperidino, 2-, 3- or 4-piperidyl, thiopyranyl, 1,4-oxazinyl, 1,4-thiazinyl, 1,3-thiazinyl, piperazinyl, triazinyl, 3- or 4-pyridazinyl, pyrazinyl, N-oxido-3- or 4-pyridazinyl, etc.; a di-cyclic or tri-cyclic, condensed heterocyclic group having 1 to 4 hetero atoms selected from, for example, oxygen, sulfur and nitrogen atoms, in addition to carbon atoms (preferably, a group to be formed by condensing the above-mentioned 5-membered or 6-membered cyclic group with one or two 5-membered or 6-membered cyclic groups each optionally having 1 to 4 hetero atoms selected from, for example, oxygen, sulfur and nitrogen atoms, in addition to carbon atoms), such as indolyl, benzofuryl, benzothiazolyl, benzoxazolyl, benzimidazolyl, quinolyl, isoquinolyl, phthalazinyl, quinazolinyl, quinoxalinyl, indolidinyl, quinolidinyl, 1,8-naphthyridinyl, dibenzofuranyl, carbazolyl, acridinyl, phenanthridinyl, chromanyl, phenothiazinyl, phenoxazinyl, etc. Of these, preferred are 5-membered to 7-membered (preferably, 5-membered or 6-membered) heterocyclic groups each having 1 to 3 hetero atoms selected from, for example, oxygen, sulfur and nitrogen atoms, in addition to carbon atoms.

[0012]

The substituents for the "heterocyclic group" of the "optionally substituted heterocyclic group"

include, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), a lower alkyl group (e.g., a C_{1-6} alkyl group, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.), a cycloalkyl group (e.g., a C_{3-6} cycloalkyl group, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.), a lower alkynyl group (e.g., a C_{2-6} alkynyl group, such as ethynyl, 1-propynyl, propargyl, etc.), a lower alkenyl group (e.g., a C_{2-6} alkenyl group, such as vinyl, allyl, isopropenyl, butenyl, isobutenyl, etc.), an aralkyl group (e.g., a C_{7-11} aralkyl group, such as benzyl, α-methylbenzyl, phenethyl, etc.), an aryl group (e.g., a C_{6-10} aryl group, such as phenyl, naphthyl, etc., preferably phenyl), a lower alkoxy group (e.g., a C_{1-6} alkoxy group, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, etc.), an aryloxy group (e.g., a C_{6-10} aryloxy group, such as phenoxy, etc.), a lower alkanoyl group (e.g., a C_{1-6} alkanoyl group, such as formyl, acetyl, propionyl, butyryl, isobutyryl, etc.), an arylcarbonyl group (e.g., a C_{6-10} arylcarbonyl group, such as benzoyl, naphthoyl, etc.), a lower alkanoyloxy group (e.g., a C_{1-6} alkanoyloxy group, such as formyloxy, acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, etc.), an arylcarbonyloxy group (e.g., a C_{6-10} arylcarbonyloxy group, such as benzoyloxy, naphthoyloxy, etc.), a carboxyl group, a lower alkoxycarbonyl group (e.g., a C_{1-6} alkoxy-carbonyl group, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, etc.), an aralkyloxycarbonyl group (e.g., a C_{7-11} aralkyloxycarbonyl group, such as benzyloxycarbonyl,

etc.), a carbamoyl group, a mono-, di- or tri-halogeno-lower alkyl group (e.g., a mono-, di- or tri-halogeno-C_{1-4} alkyl group, such as chloromethyl, dichloromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, etc.), an oxo group, an amidino group, an imino group, an amino group, a mono-lower alkylamino group (e.g., a mono-C_{1-4} alkylamino group, such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), a di-lower alkylamino group (e.g., a di-C_{1-4} alkylamino group, such as dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, etc.), a 3-membered to 6-membered cyclic amino group optionally having 1 to 3 hetero atoms selected from, for example, oxygen, sulfur and nitrogen atoms, in addition to carbon atoms and one nitrogen atom (e.g., a 3-membered to 6-membered cyclic amino group such as aziridinyl, azetidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, imidazolyl, pyrazolyl, imidazolidinyl, piperidyl, morpholinyl, dihydropyridyl, pyridyl, N-methylpiperazinyl, N-ethylpiperazinyl, etc.), an alkylenedioxy group (e.g., a C_{1-3} alkylenedioxy group, such as methylenedioxy, ethylenedioxy, etc.), a hydroxyl group, a nitro group, a cyano group, a mercapto group, a sulfo group, a sulfino group, a phosphono group, a sulfamoyl group, a monoalkylsulfamoyl group (e.g., a mono-C_{1-6} alkylsulfamoyl group, such as N-methylsulfamoyl, N-ethylsulfamoyl, N-propylsulfamoyl, N-isopropylsulfamoyl, N-butylsulfamoyl, etc.), a dialkylsulfamoyl group (e.g., a di-C_{1-6} alkylsulfamoyl group, such as N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N,N-dipropylsulfamoyl, N,N-dibutylsulfamoyl, etc.), an alkylthio group (e.g., C_{1-6} alkylthio group, such as methylthio, ethylthio,

propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio, etc.), an arylthio group (e.g., a C_{6-10} arylthio group, such as phenylthio, naphthylthio, etc.), a lower alkylsulfinyl group (e.g., a C_{1-6} alkylsulfinyl group, such as methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl, etc.), an arylsulfinyl group (e.g., a C_{6-10} arylsulfinyl group, such as phenylsulfinyl, naphthylsulfinyl, etc.), a lower alkylsulfonyl group (e.g., a C_{1-6} alkylsulfonyl group, such as methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, etc.), an arylsulfonyl group (e.g., a C_{6-10} arylsulfonyl group, such as phenylsulfonyl, naphthylsulfonyl, etc.), etc.

The "heterocyclic group" of the "optionally substituted heterocyclic group" may have 1 to 5, preferably 1 to 3 substituents selected from, for example, those mentioned above, at any substitutable positions in the group. In the case that the group has two or more substituents, these substituents may be the same or different.

[0013]

The terminology "optionally substituted amino group" as referred to herein includes amino groups each optionally having one or two substituents of, for example, the above-mentioned "optionally substituted hydrocarbon groups", etc. Preferred substituents for the "amino group" include, for example, an optionally substituted C_{1-6} alkyl group, an optionally substituted C_{6-10} aryl group, etc. The substituents which the "C_{1-6} alkyl group" or the "C_{6-10} aryl group" may optionally have are, for example the same ones as the above-mentioned "hydrocarbon group" may optionally have.

[0014]

The term "lower alkyl group" for the terminology

"optionally substituted lower alkyl group" as referred to herein indicates a C_{1-6} alkyl group, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, etc. It may optionally have 1 to 3 substituents, such as the same ones as the above-mentioned "hydrocarbon group" may optionally have.

The term "lower alkoxy group" in the terminology "optionally substituted lower alkoxy group" as referred to herein indicates a C_{1-6} alkoxy group such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, etc. It may optionally have 1 to 3 substituents, such as the same ones as the above-mentioned "hydrocarbon group" may optionally have.
[0015]

The terminology "optionally substituted benzene ring" as referred to herein indicates a benzene ring which may optionally have one or two substituents selected from, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), an optionally substituted hydrocarbon group, an optionally substituted amino group, an amido group (e.g., a C_{1-6} acylamino group, such as acetamido, etc., preferably a C_{1-6} alkanoylamino group, etc.), an optionally substituted lower alkoxy group, a lower alkylenedioxy group (e.g., a C_{1-6} alkylenedioxy group, such as methylenedioxy, ethylenedioxy, etc.), etc., at any substitutable positions in the ring.

For these "optionally substituted hydrocarbon group" and "optionally substituted amino group", the same ones as those described in detail hereinabove are referred to. In the case that these "hydrocarbon group", "lower alkoxy group" and "amino group" each have two or more substituents, these substituents may be the same or different.

The "optionally substituted benzene ring" is preferably a benzene ring optionally substituted by 1 to 3 substituents selected from, for example, a halogen atom (e.g., fluorine, chlorine, etc.), a C_{1-6} alkyl group (e.g., methyl, ethyl, etc.) and a mono-C_{1-6} alkylamino group.

[0016]

In the above-mentioned formulae, R^1 represents an optionally substituted hydrocarbon group, an optionally substituted amino group or an optionally substituted heterocyclic group.

The "hydrocarbon group" of the "optionally substituted hydrocarbon group" to be represented by R^1 is preferably an alkyl group (e.g., a C_{1-6} alkyl group, such as methyl, ethyl, propyl, isopropyl, etc.), an alkenyl group (e.g., C_{2-6} alkenyl group, such as vinyl, etc.), an alkynyl group (e.g., a C_{2-6} alkynyl group, such as ethynyl), a cycloalkyl group (e.g., a C_{3-6} cycloalkyl group, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.), or an aryl group (e.g., a C_{6-14} aryl group, such as phenyl, etc.), especially preferably an alkyl group (e.g., a C_{1-6} alkyl group, such as methyl, etc.) or a cycloalkyl group (e.g., a C_{3-6} cycloalkyl group, such as cyclopropyl, etc.) These "alkyl group", "alkenyl group", "alkynyl group", "cycloalkyl group" and "aryl group" each may have 1 to 5, preferably 1 to 3 substituents, such as the same ones as the above-mentioned "hydrocarbon group" may optionally have, preferably halogen atoms, such as fluorines, etc.

[0017]

Preferred substituents for the "optionally substituted amino group" to be represented by R^1, are one or two substituents of, for example, an optionally

substituted lower alkyl group and an optionally substituted aryl group, more preferably one substituent of an optionally substituted lower alkyl group. The "lower alkyl group" may be a C_{1-6} alkyl group, including, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, etc. The "lower alkyl group" may optionally have from 1 to 3 substituents, such as the same ones as the above-mentioned "hydrocarbon group". The "aryl group" may be a C_{6-10} aryl group, including, for example, phenyl, etc. The "aryl group" may optionally have from 1 to 5, preferably from 1 to 3 substituents, such as the same one as the above-mentioned "hydrocarbon group" may optionally have, preferably those selected from, for example, halogen atoms such as fluorine, chlorine, etc., and C_{1-6} alkoxy groups such as methoxy, ethoxy, etc. The "optionally-substituted amino group" is generally a phenylamino group substituted by, for example, 1 to 3 lower alkoxy groups (e.g., C_{1-4} alkoxy groups, such as methoxy, etc.), or an amino group mono-substituted by a lower alkyl group (e.g., a C_{1-4} alkyl group, such as methyl, ethyl, propyl, butyl, tert-butyl, etc.)

[0018]

The "heterocyclic group" of the "optionally substituted heterocyclic group" to be represented by R^1 is, for example, preferably a 5-membered or 6-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur atoms in addition to carbon atoms. Concretely, it includes 1-, 2- or 3-pyrrolidinyl, 2- or 4-imidazolinyl, 2-, 3- or 4-pyrazolidinyl, piperidino, 2-, 3- or 4-piperidyl, 1- or 2-piperazinyl, morpholinyl, 2- or 3-thienyl, 2-, 3- or 4-pyridyl, 2- or 3-furyl, pyrazinyl, 2-pyrimidinyl, 3-

pyrrolyl, 3-pyridazinyl, 3-isothiazolyl, 3-isoxazolyl, etc. Especially preferably, it is a 6-membered nitrogen-containing heterocyclic group (e.g., pyridyl, etc.) or the like.

Preferred substituents for the "optionally substituted heterocyclic group" to be represented by R^1 include, for example, a halogen atom (e.g., chlorine, fluorine, etc.), a C_{1-6} alkyl group (e.g., methyl, ethyl, etc.), a C_{1-6} alkoxy group (e.g., methoxy, ethoxy, etc.), an aralkyloxycarbonyl group (e.g., a C_{7-12} aralkyloxy-carbonyl group, such as benzyloxycarbonyl, etc.), etc.

[0019]

R^1 is, for example, preferably (i) an optionally substituted lower alkyl group, (ii) an optionally substituted lower cycloalkyl group, (iii) an optionally substituted lower alkenyl group, (iv) an optionally substituted aryl group, (v) an optionally substituted mono- or di-lower alkylamino group, (vi) an optionally substituted arylamino group or (vii) an optionally substituted, 5- or 6-membered nitrogen-containing heterocyclic group.

The "lower alkyl group" is preferably a C_{1-6} alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, etc. The "lower cycloalkyl group" is preferably a C_{3-6} cycloalkyl group, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc. The "lower alkenyl group" is preferably a C_{2-6} alkenyl group, such as vinyl, 1-propenyl, butenyl, etc. The "aryl group" is preferably a C_{6-10} aryl group, such as phenyl, 1-naphthyl, 2-naphthyl, etc. The "lower alkylamino group" is preferably a mono- or di-C_{1-6} alkylamino group, such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, tert-butylamino,

dimethylamino, diethylamino, methylethylamino, etc. The "arylamino group" is preferably a C_{6-10} arylamino group, such as phenylamino, etc. The "5- or 6-membered nitrogen-containing heterocyclic group" is, for example, preferably 2-, 3- or 4-pyridyl or the like. These groups may each optionally have 1 to 5 substituents such as those referred to the mentioned-above "hydrocarbon group" may optionally have.
[0020]

More preferably, R^1 is (i) a C_{1-6} alkyl group optionally substituted by 1 to 4 substituents selected from a halogen atom and a C_{1-6} alkoxy group, (ii) a C_{3-6} cycloalkyl group, (iii) a C_{2-6} alkenyl group, (iv) a C_{6-10} aryl group optionally substituted by 1 to 4 substituents selected from a C_{1-6} alkoxy group, a nitro group, a halogeno-C_{1-6} alkylcarbonylamino group and a halogen atom, (v) a mono- or di-C_{1-6} alkylamino group, (vi) a C_{6-10} arylamino group optionally substituted by one to three C_{1-6} alkoxy groups, or (vii) a 6-membered nitrogen-containing heterocyclic group optionally substituted by one or two C_{7-11} aralkyloxycarbonyl groups. Even more preferably, R^1 is an optionally halogenated C_{1-6} alkyl group (e.g., methyl, chloromethyl, difluoromethyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, propyl, 3,3,3-trifluoropropyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, 4,4,4-trifluorobutyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl, hexyl, 6,6,6-trifluorohexyl, etc.), a C_{3-6} cycloalkyl group (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.), or a mono-C_{1-6} alkylamino group (e.g., methylamino, ethylamino, propylamino, isopropylamino,

butylamino, tert-butylamino, etc.) Among ohters, R^1 is preferably an optionally halogenated C_{1-6} alkyl group or a mono-C_{1-6} alkylamino group, especially a halogeno-C_{1-3} alkyl group (e.g., chloromethyl, etc.)

[0021]

In the above-mentioned formulae, R^2 represents a hydrogen atom or an optionally substituted hydrocarbon group.

The "hydrocarbon group" for R^2 includes, for example, an aliphatic hydrocarbon group, a mono-cyclic saturated hydrocarbon group, an aromatic hydrocarbon group, etc., and it preferably has 1 to 16 carbon atoms. Concretely, it includes an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, an aryl group, etc.

The "alkyl group" is preferably a lower alkyl group, which is generally a C_{1-6} alkyl group and includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.

The "alkenyl group" is preferably a lower alkenyl group, which is generally a C_{2-6} alkenyl group and includes, for example, vinyl, 1-propenyl, allyl, isopropenyl, butenyl, isobutenyl, etc.

The "alkynyl group" is preferably a lower alkenyl group, which is generally a C_{2-6} alkynyl group and includes, for example, ethynyl, propargyl, 1-propynyl, etc.

The "cycloalkyl group" is preferably a lower cycloalkyl group, which is generally a C_{3-6} cycloalkyl group and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

The "aryl group" is preferably a C_{6-14} aryl group, including, for example, phenyl, xylyl, 1-naphthyl, 2-

naphthyl, biphenylyl, 2-indenyl, 2-anthryl, etc., and is more preferably a phenyl group.

These "alkyl group", "alkenyl group", "alkynyl group", "cycloalkyl group" and "aryl group" each may have 1 to 5, preferably from 1 to 3 substituents such as the same ones as the above-mentioned "hydrocarbon group" may optionally have.

In particular, R^2 is preferably a hydrogen atom or an optionally-substituted lower (C_{1-6}) alkyl group, more preferably a hydrogen atom or a lower (C_{1-6}) alkyl group, even more preferably a hydrogen atom.

[0022]

In the above-mentioned formulae, R^3 represents a hydrogen atom, an optionally substituted hydrocarbon group, or an optionally substituted heterocyclic group.

The "hydrocarbon group" of the "optionally substituted hydrocarbon group" to be represented by R^3 is preferably an alkyl group (e.g., a C_{1-6} alkyl group, such as methyl, ethyl, propyl, isopropyl, etc.), an alkenyl group (e.g., a C_{2-6} alkenyl group, such as vinyl, etc.), an alkynyl group (e.g., a C_{2-6} alkynyl group, such as ethynyl, etc.), a cycloalkyl group (e.g., a C_{3-6} cycloalkyl group, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.), or an aryl group (e.g., a C_{6-14} aryl group, such as phenyl, etc.) It is especially preferably an alkyl group (e.g., a C_{1-6} alkyl group such as methyl, etc.), or an aryl group (e.g., a C_{6-14} aryl groups such as phenyl, etc.) These "alkyl group", "alkenyl group", "alkynyl group", "cycloalkyl group" and "aryl group" each may optionally have from 1 to 5, preferably from 1 to 3 substituents such as the same ones or the mentioned-above "hydrocarbon grou"p may optionally have (e.g., halogen atoms such as fluorines, etc.)

[0023]

The "heterocyclic group" of the "optionally substituted heterocyclic group" to be represented by R^3 is preferably a 5- or 6-membered heterocyclic group having 1 to 3 hetero atoms selected from nitrogen, oxygen and sulfur atoms, in addition to carbon atoms. Concretely, it includes, for example, 1-, 2- or 3-pyrrolidinyl, 2- or 4-imidazolinyl, 2-, 3- or 4-pyrazolidinyl, piperidino, 2-, 3- or 4- piperidyl, 1- or 2-piperazinyl, morpholinyl, 2- or 3-thienyl, 2-, 3- or 4-pyridyl, 2- or 3-furyl, pyrazinyl, 2-pyrimidinyl, 3-pyrrolyl, 3-pyridazinyl, 3-isothiazolyl, 3-isoxazolyl, etc. Especially preferably, it is a 6-membered nitrogen-containing heterocyclic group (e.g., pyridyl, etc.), etc.

Preferred substituents for the "optionally substituted heterocyclic group" to be represented by R^3 include, for example, a halogen atom (e.g., chlorine, fluorine, etc.), a C_{1-6} alkyl group (e.g., methyl, ethyl), a C_{1-6} alkoxy group (e.g., methoxy, ethoxy, etc.), an aralkyloxycarbonyl group (e.g., a C_{7-12} aralkyloxy-carbonyl group, such as benzyloxycarbonyl, etc.), etc.

R^3 is, for example, preferably (i) a hydrogen atom, (ii) an optionally substituted lower alkyl group, (iii) an optionally substituted aryl group, etc.

More preferably, R^3 is, for example, (i) a hydrogen atom, (ii) a lower alkyl group, (iii) an aryl group, etc.

[0024]

In the above-mentioned formulae, X represents CHR^4, NR^4 (in which R^4 represents a hydrogen atom or an optionally substituted hydrocarbon group), O or S.

The "hydrocarbon group" for R^4 includes, for

example, an aliphatic hydrocarbon group, a mono-cyclic saturated hydrocarbon group, an aromatic hydrocarbon group, etc., and it preferably has 1 to 16 carbon atoms. Concretely, it includes, for example, an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, an aryl group, etc.

The "alkyl group" is preferably a lower alkyl group, which is generally a C_{1-6} alkyl group and includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.

The "alkenyl group" is preferably a lower alkenyl group, which is generally a C_{2-6} alkenyl group and includes, for example, vinyl, 1-propenyl, allyl, isopropenyl, butenyl, isobutenyl, etc.

The "alkynyl group" is preferably a lower alkynyl group, which is generally a C_{2-6} alkynyl group and includes, for example, ethynyl, propargyl, 1-propynyl, etc.

The "cycloalkyl group" is preferably a lower cycloalkyl group, which is generally a C_{3-6} cycloalkyl group and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

The "aryl group" is preferably a C_{6-14} aryl group, including, for example, phenyl, xylyl, 1-naphthyl, 2-naphthyl, biphenylyl, 2-indenyl, 2-anthryl, etc., and is more preferably a phenyl group.

These "alkyl group", "alkenyl group", "alkynyl group", "cycloalkyl group" and "aryl group" each may have from 1 to 5, preferably from 1 to 3 substituents such as the same ones as the above-mentioned "hydrocarbon group" may optionally have.

Preferably, R^4 is a hydrogen atom, or an optionally substituted lower (C_{1-6}) alkyl group, even

more preferably a hydrogen atom.

X is preferably CHR^4 or NR^4 (where R^4 is as defined above).

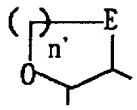
In the above-mentioned formulae, Y represents C, CH or N, provided that when X is CH_2, Y is C or CH. Preferably, Y represents C or CH.

[0025]

In the above-mentioned formulae, ring A represents an optionally substituted, 5- to 7-membered oxygen-containing heterocyclic ring.

The "5- to 7-membered, oxygen-containing heterocyclic ring" includes 5- to 7-membered (preferably 5- or 6-membered) heterocyclic groups optionally having 1 to 3 hetero atoms, that are the same or different, selected from nitrogen, oxygen and sulfur atoms, in addition to carbon and oxygen atoms, etc.

Ring A is preferably



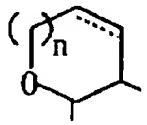
wherein E represents (i) CH_2CH_2, (ii) CH=CH, (iii) CH_2O, (iv) OCH_2, (v) $CH_2S(O)_{q'}$ (where q' represents an integer of 0 to 2), (vi) $S(O)_{q'}CH_2$ (q' is as defined above), (vii) CH_2NH, (viii) $NHCH_2$, (ix) N=N, (x) CH=N or (xi) N=CH; and n' represents an integer of 0 to 2.

E is preferably (i) CH_2CH_2, (ii) CH=CH, (iii) CH_2O, (iv) OCH_2, (v) CH_2NH, (vi) $NHCH_2$, (vii) N=N, (viii) CH=N or (ix) N=CH, especially preferably (i) CH_2CH_2 or (ii) CH=CH.

Concretely, ring A includes, for example, a 5-membered oxygen-containing heterocyclic group such as 2,3-dihydrofuran, furan, 1,3-dioxole, oxazoline,

isoxazole, 1,2,3-oxadiazole, oxazole, etc., or a 6-membered oxygen-containing heterocyclic group such as 2H-3,4-dihydropyran, 2H-pyran, 2,3-dehydro-1,4-dioxane, 2,3-dehydromorpholine, etc.

More preferably, ring A is



wherein n is as defined above.

Concretely, 2,3-dihydrofuran, furan, 2H-3,4-dihydropyran and 2H-pyran are preferably used.

[0026]

Substituents on ring A or ring A' include, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), a lower alkyl group (e.g., a C_{1-6} alkyl group, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.), a cycloalkyl group (e.g., a C_{3-6} cycloalkyl group, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.), a lower alkynyl group (e.g., a C_{2-6} alkynyl group, such as ethynyl, 1-propynyl, propargyl, etc.), a lower alkenyl group (e.g., a C_{2-6} alkenyl group, such as vinyl, allyl, isopropenyl, butenyl, isobutenyl, etc.), an aralkyl group (e.g., a C_{7-11} aralkyl group, such as benzyl, α-methylbenzyl, phenethyl, etc.), an aryl group (e.g., a C_{6-10} aryl group, such as phenyl, naphthyl, etc., preferably phenyl), a lower alkoxy group (e.g., a C_{1-6} alkoxy group, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, etc.), an aryloxy group (e.g., a C_{6-10} aryloxy group, such as phenoxy, etc.), a lower alkanoyl group (e.g., a C_{1-6} alkanoyl group, such as formyl, acetyl, propionyl,

butyryl, isobutyryl, etc.), an arylcarbonyl group (e.g., a C_{6-10} arylcarbonyl group, such as benzoyl, naphthoyl, etc.), a lower alkanoyloxy group (e.g., a C_{1-6} alkanoyloxy group, such as formyloxy, acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, etc.), an arylcarbonyloxy group (e.g., a C_{6-10} arylcarbonyloxy group, such as benzoyloxy, naphthoyloxy, etc.), a carboxyl group, a lower alkoxycarbonyl group (e.g., a C_{1-6} alkoxy-carbonyl group, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, etc.), an aralkyloxy group (e.g., a C_{7-11} aralkyloxycarbonyl group, such as benzyloxycarbonyl, etc.), a carbamoyl group, a mono-, di- or tri-halogeno-lower alkyl group (e.g., a mono-, di- or tri-halogeno-C_{1-4} alkyl group, such as chloromethyl, dichloromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, etc.), an oxo group, an amidino group, an imino group, an amino group, a mono-lower alkylamino group (e.g., a mono-C_{1-4} alkylamino group, such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), a di-lower alkylamino group (e.g., a di-C_{1-4} alkylamino group, such as dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, etc.), a 3- to 6-membered cyclic amino group optionally having 1 to 3 hetero atoms selected from, for example, oxygen, sulfur and nitrogen atoms, in addition to carbon atoms and one nitrogen atom (e.g., a 3- to 6-membered cyclic amino group, such as aziridinyl, azetidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, imidazolyl, pyrazolyl, imidazolidinyl, piperidyl, morpholinyl, dihydropyridyl, pyridyl, N-methylpiperazinyl, N-ethylpiperazinyl, etc.), an alkylenedioxy group (e.g., a C_{1-3} alkylenedioxy group, such as methylenedioxy,

ethylenedioxy, etc.), a hydroxyl group, a nitro group, a cyano group, a mercapto group, a sulfo group, a sulfino group, a phosphono group, a sulfamoyl group, a monoalkylsulfamoyl group (e.g., a mono-C_{1-6} alkylsulfamoyl group, such as N-methylsulfamoyl, N-ethylsulfamoyl, N-propylsulfamoyl, N-isopropylsulfamoyl, N-butylsulfamoyl, etc.), a dialkylsulfamoyl group (e.g., a di-C_{1-6} alkylsulfamoyl group, such as N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N,N-dipropylsulfamoyl, N,N-dibutylsulfamoyl, etc.), an alkylthio group (e.g., a C_{1-6} alkylthio group, such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio, etc.), an arylthio group (e.g., a C_{6-10} arylthio group, such as phenylthio, naphthylthio, etc.), a lower alkylsulfinyl group (e.g., a C_{1-6} alkylsulfinyl group, such as methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl, etc.), an arylsulfinyl group (e.g., a C_{6-10} arylsulfinyl group, such as phenylsulfinyl, naphthylsulfinyl, etc.), a lower alkylsulfonyl group (e.g., a C_{1-6} alkylsulfonyl group, such as methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, etc.), an arylsulfonyl group (e.g., a C_{6-10} arylsulfonyl group, such as phenylsulfonyl, naphthylsulfonyl, etc.), etc.

The above "lower alkyl group", "lower alkenyl group", "lower alkynyl group", "lower cycloalkyl group" and "aryl group" each may optionally have the same ones as the above-mentioned 1 to 5, preferably 1 to 3 substituents such as those "hydrocarbon group" may optionally have.

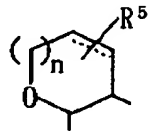
[0037]

Preferred substituents on ring A or ring A' are a halogen atom, an optionally substituted C_{1-6} alkyl

group, an optionally substituted C_{1-6} alkoxy group, a hydroxyl group, a nitro group, a cyano group, an optionally substituted amino group, etc. For the substituents in these "optionally-substituted C_{1-6} alkyl group", "optionally-substituted C_{1-6} alkoxy group" and "optionally-substituted amino group", for example, referred to are the substituents which mentioned-above "hydrocarbon group" may optionally have.

Ring A and ring A' may have 1 to 4, preferably one or two substituents selected from, for example, those mentioned above at any substitutable positions, depending on the number of the carbon atoms constituting them. If the rings each have two or more substituents, these substituents may be the same or different.

Ring A and ring A' are, for example;



wherein n is as defined mentioned above; and R^5 represents a hydrogen atom or a substituent selected from the "preferred substituents for ring A and ring A'" mentioned hereinabove. R^5 is preferably a hydrogen atom, which indicates unsubstituted ring A and ring A'.
[0038]

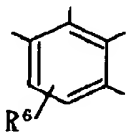
In the above-mentioned formulae, ring B represents an optionally substituted benzene ring.

For the substituents on ring B, for example, are the "substituents" mentioned hereinabove for the "optionally-substituted benzene ring". Among others, the substituents on ring B are preferably a halogen atom and an optionally substituted lower (C_{1-6}) alkyl group, more preferably a halogen atom and a lower (C_{1-6})

alkyl group (especially, methyl). As for the substituents for the "optionally substituted lower (C_{1-6}) alkyl group", for example, referred to are the same ones as the mentioned-above "hydrocarbon group" may optionally have.

Ring B may have one or two, preferably one substituent selected from those mentioned hereinabove, at any substitutable position. Where ring B has two substituents, they may be the same or different.

For example, ring B is preferably



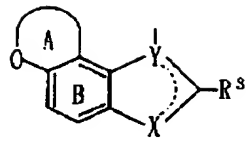
wherein R^6 represents a hydrogen atom, a halogen atom, an optionally substituted lower alkyl group (e.g., a C_{1-6} alkyl group, such as methyl, ethyl, etc.), or an optionally substituted lower (C_{1-6}) alkoxy group. R^6 is preferably a hydrogen atom, a halogen atom, or a lower (C_{1-6}) alkyl group (especially, methyl).

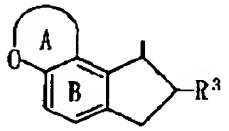
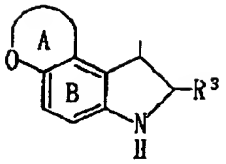
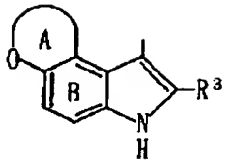
[0039]

In the above-mentioned formulae, m represents an integer of 1 to 4. Preferably, m is an integer of 1 to 3, more preferably 2 or 3, even more preferably 2.

In the above-mentioned formulae, n represents an integer of 0 to 2. Preferably, n is an integer of 0 or 1.

Preferred examples of

are 

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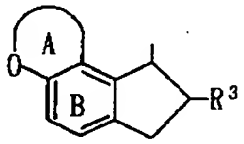
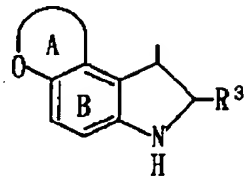
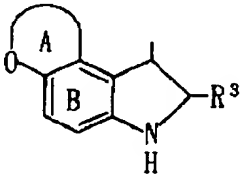
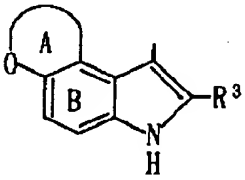



wherein the symbols are as defined above; OR

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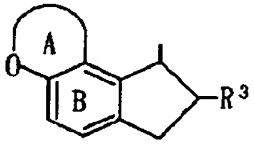

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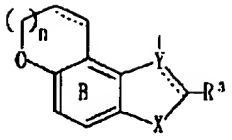

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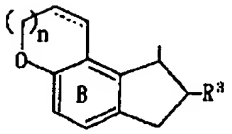
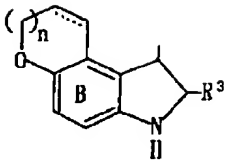
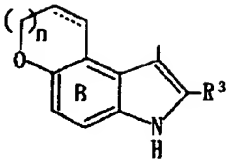

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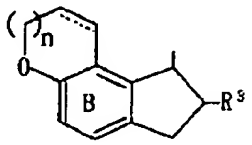
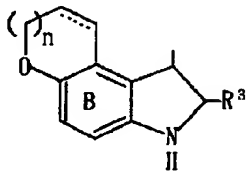
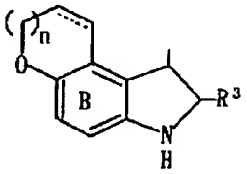
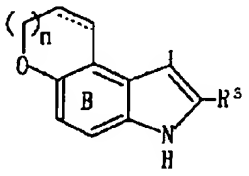
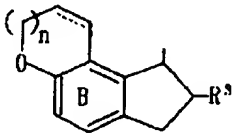



wherein the symbols are as defined above; or

wherein the symbols are as defined above.

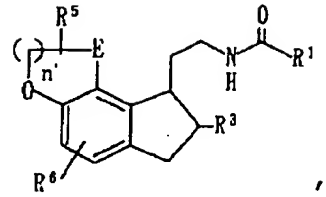
More preferred is

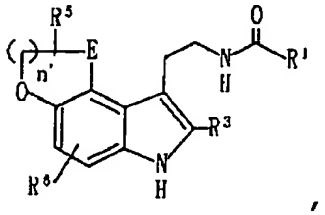


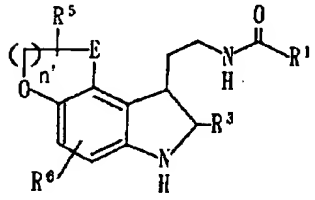
wherein the symbols are as defined above.

[0041]

Of the compound (I) of the present invention, those having the following structural formulae are especially preferred.

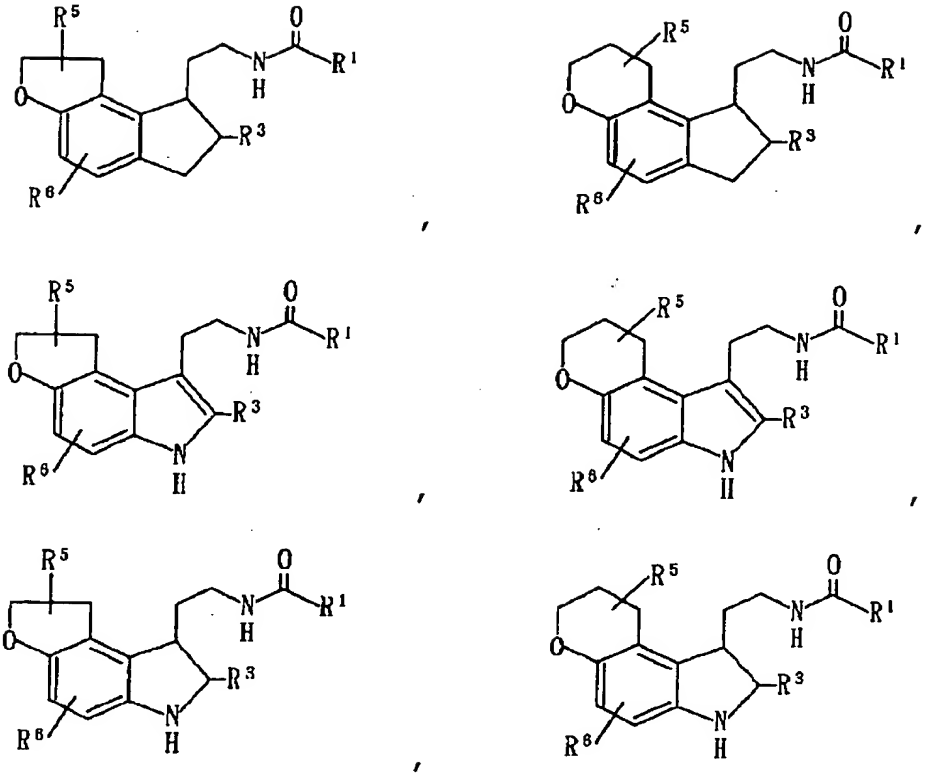






wherein the symbols are as defined above.

Preferred examples of the compound (I) include, for example, compounds of the following formulae:



wherein the symbols are as defined above.

[0042]

Also preferred examples of the compound (I) are the compound of the formula (I), in which;

R^1 is (i) an optionally substituted lower alkyl group, (ii) an optionally substituted lower cycloalkyl group, (iii) an optionally substituted lower alkenyl group, (iv) an optionally substituted aryl group, (v) an optionally substituted mono- or di-lower alkylamino group, (vi) an optionally substituted arylamino group, or (vii) an optionally substituted, 5- or 6-membered nitrogen-containing heterocyclic group;

R^2 is a hydrogen atom, or an optionally-substituted lower (C_{1-6}) alkyl group;

R^3 is (i) a hydrogen atom, (ii) an optionally

substituted lower alkyl group or (iii) an optionally substituted aryl group;

X is CHR^4 or NR^4 (where R^4 is a hydrogen atom or a lower (C_{1-6}) alkyl group);

Y is C, CH or N, provided that when X is CH_2, Y is C or CH;

$\overline{-----}$ represents a single bond or a double bond;

ring A is an optionally substituted, 5- to 7-membered oxygen-containing heterocyclic ring;

ring B is an optionally substituted benzene ring; and

m is 1 or 2.

Even more preferably, the compound in which

R^1 is (i) a C_{1-6} alkyl group optionally substituted by 1 to 4 substituents selected from halogens and a C_{1-6} alkoxy group, (ii) a C_{3-6} cycloalkyl group, (iii) a C_{2-6} alkenyl group, (iv) a C_{6-10} aryl group optionally substituted by 1 to 4 substituents selected from a C_{1-6} alkoxy group, nitro, a halogeno-C_{1-6} alkyl-carbonylamino groups and halogen, (v) a mono- or di-C_{1-6} alkylamino group, (vi) a C_{6-10} arylamino group optionally substituted by from one to three C_{1-6} alkoxy groups, or (vii) a 6-membered, nitrogen-containing heterocyclic group optionally substituted by one or two C_{7-11} aralkyloxycarbonyl groups;

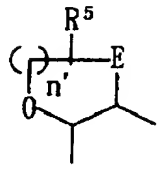
R^2 is a hydrogen atom or a lower (C_{1-6}) alkyl group;

R^3 is (i) a hydrogen atom, (ii) a lower alkyl group or (iii) an aryl group;

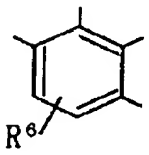
X is CHR^4 or NR^4 (where R^4 is a hydrogen atom or a lower (C_{1-6}) alkyl group);

Y is C, CH or N, provided that when X is CH_2, Y is C or CH;

----- represents a single bond or a double bond;
ring A is



wherein the symbols are as defined above;
ring B is



wherein R^6 represents a hydrogen atom, a halogen atom or a lower (C_{1-6}) alkyl group; and
m is 1 or 2.

[0044]

Preferable examples of the compounds (I), (II) and their salts include.

N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]butyramide,

N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide,

N-[2-(3,7,8,9-tetrahydropyrano[3,2-e]indol-1-yl)ethyl]propionamide,

N-[2-(3,7,8,9-tetrahydropyrano[3,2-e]indol-1-yl)ethyl]butyramide,

N-[2-(1,2,3,7,8,9-hexahydropyrano[3,2-e]indol-1-yl)ethyl]propionamide,

N-[2-(1,2,3,7,8,9-hexahydropyrano[3,2-e]indol-1-yl)ethyl]butyramide,

N-[2-(4-fluoro-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]butyramide,

N-[2-(4-fluoro-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide.

[0045]

Salts of the compound (I) of the present invention include, for example, pharmaceutically acceptable salts thereof. For example, mentioned are salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids, salts with basic or acidic amino acids, etc. Preferred examples of salts with inorganic bases include, for example, alkali metal salts such as sodium salts, potassium salts, etc., alkaline earth metal salts such as calcium salts, magnesium salts, etc., as well as aluminium salts, ammonium salts, etc. Preferred examples of salts with organic bases include, for example, salts with trimethylamine, triethylamine, pyridine, picoline, 2,6-lutidine, ethanolamine, diethanolamine, triethanolamine, cyclohexylamine, dicyclohexylamine, N,N'-dibenzylethylenediamine, etc. Preferred examples of salts with inorganic acids include, for example, salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc. Preferred examples of salts with organic acids include, for example, salts with formic acid, acetic acid, trifluoroacetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc. Preferred examples of salts with basic amino acids include, for example, salts with arginine, lysine, ornithine, etc. Preferred examples of salts with acidic amino acids include, for example, salts with aspartic acid, glutamic acid, etc.

Above all, preferred are pharmaceutically

acceptable salts which include, for example, salts of compounds (I) having basic functional group(s) with inorganic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc., or with organic acids such as acetic acid, phthalic acid, fumaric acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid, etc., as well as salts of compound (I) having acidic functional group(s) with alkali metals such as sodium salts, potassium salts, etc., or with alkaline earth metals such as calcium salts, magnesium salts, etc., and also ammonium salts therewith, etc.

[0046]

A process for producing the compound (I) and a salt thereof (compound (I) as referred to hereinunder shall encompass its salts, if appropriate) of the present invention are mentioned below.

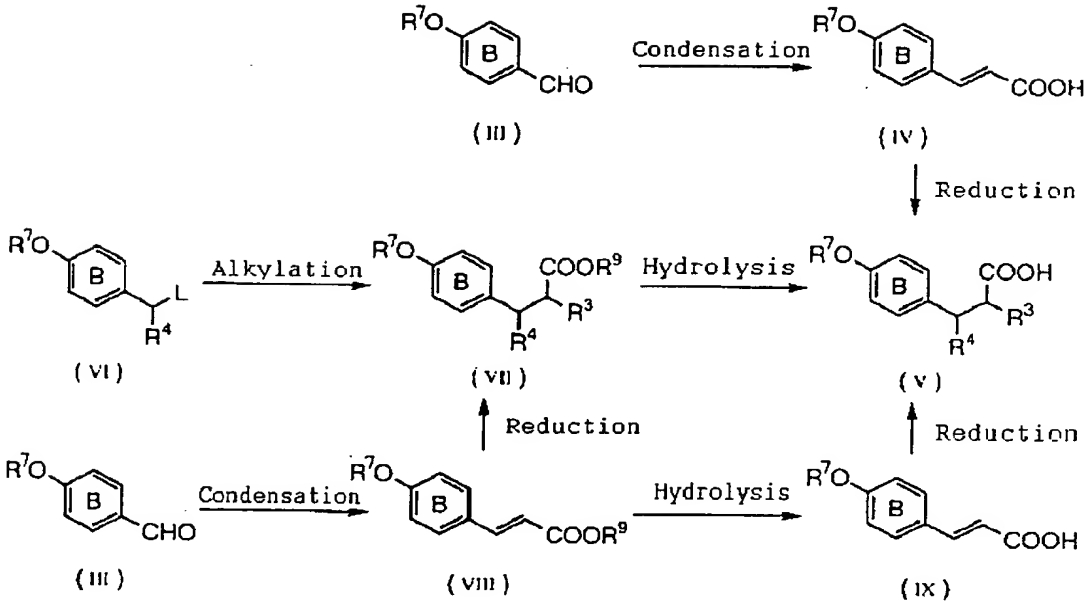
Compound (I) of the present invention can be produced, for example, in accordance with the reaction processes mentioned below or in the same manner as in the illustrated reaction schemes.

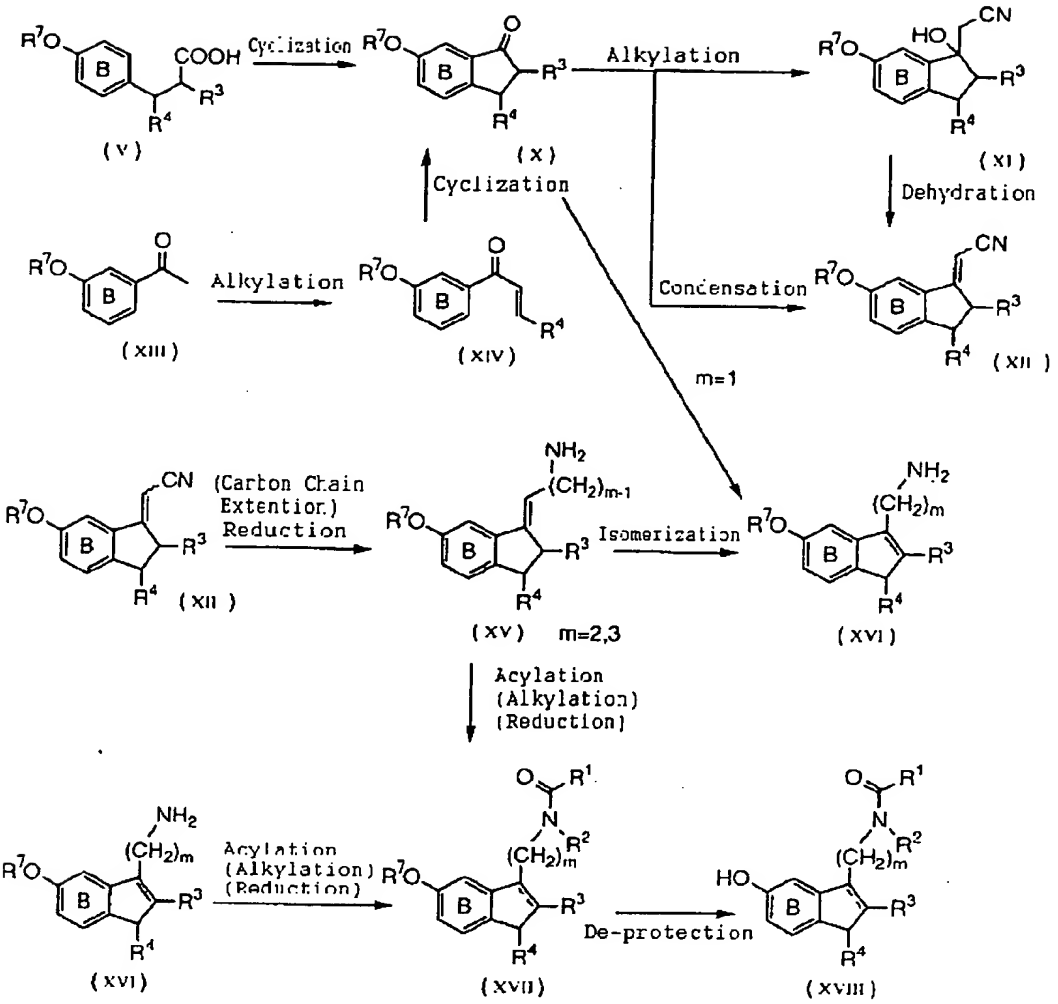
Compounds (III) to (XXXXIX) in the following reaction schemes encompass their salts, for which the salts of the compound (I) mentioned hereinabove are referred to.

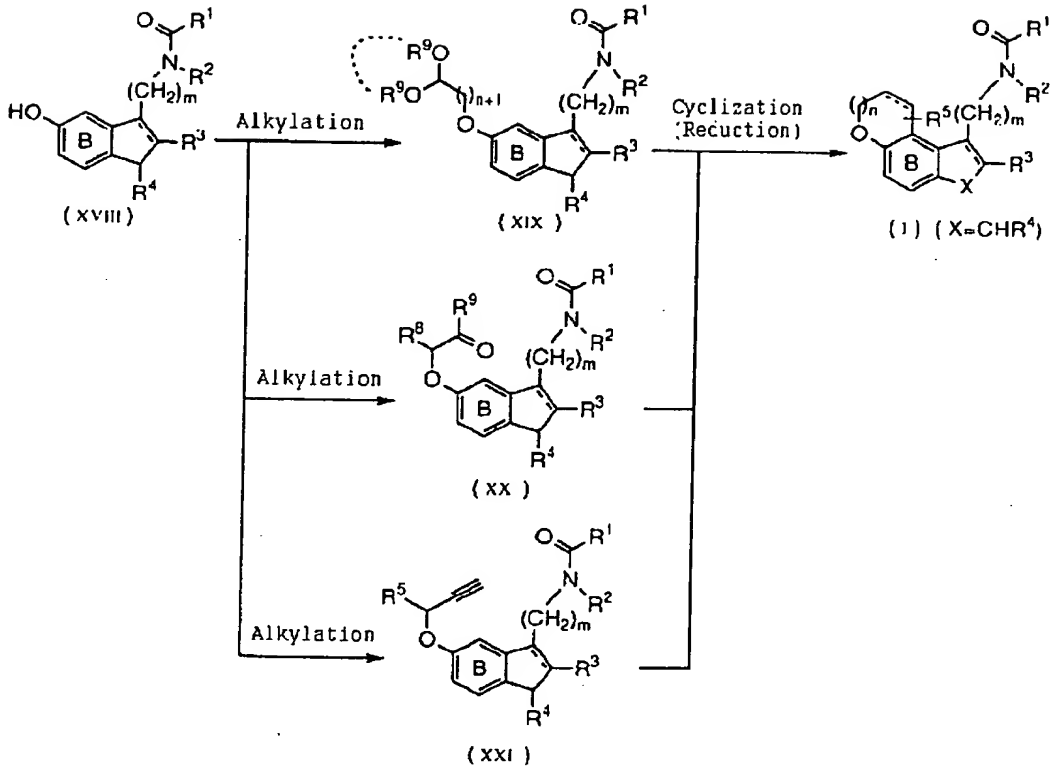
The symbols for the compounds in the following reaction schemes are as defined those mentioned above.

[0047]

Reaction Process. 1:




Cyclization
Alkylation
Dehydration
Cyclization
Alkylation
Condensation
m=1
(Carton Chain Extention) Reduction
Isomerization
m=2,3
Acylation (Alkylation) (Reduction)
Acylation (Alkylation) (Reduction)
De-protection



[0048]

Compound (III) can be produced using per se known methods, for example, using the methods described in Jikken Kagaku Koza (Lectures on Experimental Chemistry), 4th Ed., Vol. 21, pp. 1-148 (edited by the Japan Chemical Society) or methods analogous thereto.

Compound (VI) (wherein L represents a leaving group such as a halogen atom, an alkylsulfonyl group, an alkylsulfonyloxy group, an arylsulfonyloxy group, etc.; R^7 represents an optionally substituted hydrocarbon group) can be produced using per se known methods, for example, using the methods described in Bull. Chem. Soc. Japan, Vol. 64, p. 1410 (1991), J. Indian Chem. Soc., Vol. 66, p. 656 (1989), and J. Med. Chem., Vol. 29, p. 1586 and p. 1904 (1986), or methods analogous thereto.

[0049]

Compound (XIII) can be produced using per se known methods, for example, using the methods described in J. Chem. Soc., p. 4691 (1963), Chem. Lett., p. 165 (1986) or methods analogous thereto.

The halogen atom to be represented by L includes, for example, fluorine, chlorine, bromine, iodine, etc. The alkylsulfonyl group to be represented by L includes, for example, a C_{1-5} alkylsulfonyl group (e.g., methanesulfonyl, ethanesulfonyl, etc.), etc. The alkylsulfonyloxy group to be represented by L includes, for example, an optionally halogenated C_{1-5} alkylsulfonyloxy group (e.g., methanesulfonyloxy, ethanesulfonyloxy, trichloromethanesulfonyloxy, etc.), etc. The arylsulfonyloxy group to be represented by L includes, for example, an optionally substituted benzenesulfonyloxy group (e.g., p-toluenesulfonyloxy, benzenesulfonyloxy, etc.), etc.

For the compounds in the above-mentioned reaction schemes, commercial products, if available, can be directly used.

[0050]

Compound (IV) can be produced from compound (III) and malonic acid through the Knoevenagel condensation thereof in the presence of a base. One mol of compound (III) is reacted with approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 2.0 mols of malonic acid. The base includes, for example, inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc. The base is used in an amount of approximately from 0.1 to 5.0 mols, preferably

approximately from 0.1 to 1.0 mol per mol of compound (III). The reaction is advantageously conducted in a solvent inert thereto. The solvent is not specifically defined so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; organic acids such as formic acid, acetic acid, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc. Mixed solvents comprising them are also preferably used. The reaction time varies, depending on the reagents and solvents used, and is generally from 30 minutes to 24 hours, preferably from 30 minutes to 4 hours. The reaction temperature is generally from 0 to 100°C, preferably from 0 to 70°C. The product (IV) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0051]

Compound (VIII) (in which R^8 represents a hydrocarbon group) can be obtained by reacting a phosphonato-carbanion, which is produced by the treatment of a trialkyl phosphonoacetate with a base, with compound (III). This is obtained as a single E-form or Z-form configurational isomer or as a mixture of such E- and Z-isomers. The trialkyl phosphonoacetate includes, for example, ethyl trialkyl phosphonoacetate, etc. One mol of compound (III) is reacted with approximately from 1.0 to 3.0 mols, preferably approximately from 1.0 to 1.5 mols of a

trialkyl phosphonoacetate. The base includes, for example, alkali metal hydrides such as sodium hydride, potassium hydride, etc., metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 1.5 mols, per mol of compound (III). The reaction is advantageously conducted in a solvent inert thereto. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; sulfoxides such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 1 hour to 50 hours, preferably from 1 hour to 10 hours. The reaction temperature is generally from -78 to 200°C, preferably from 0 to 150°C. The mixture of isomers of compound (VIII) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, for example, through recrystallization, distillation, chromatography or the like.

[0052]

Compound (IX) can be produced by hydrolyzing the ester moiety of compound (VIII) with an acid or base. For the acid hydrolysis, generally used are mineral acids such as hydrochloric acid, sulfuric acid, etc.;

Lewis acids such as boron trichloride, boron trifluoride, etc.; a combination of a Lewis acid and a thiol or sulfide; organic acids such as trifluoroacetic acid, p-toluenesulfonic acid, etc. For the alkali hydrolysis, generally used are metal hydroxides such as sodium hydroxide, potassium hydroxide, barium hydroxide, etc.; metal carbonates such as sodium carbonate, potassium carbonate, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.; organic bases such as triethylamine, imidazole, formamidine, etc. These acids and bases are used at approximately from 0.5 to 10 mols, preferably approximately from 0.5 to 3.0 mols per mol of compound (VIII). The reaction is advantageously conducted either in the absence of a solvent or the presence of a solvent inert to the reaction. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; aromatic hydrocarbons such as benzene, toluene, etc.; saturated hydrocarbons such as cyclohexane, hexane, etc.; organic acids such as formic acid, acetic acid, etc.; ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; ketones such as acetone, methylethylketone, etc.; sulfoxides such as dimethylsulfoxide, etc.; water, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 10 minutes to 60 hours, preferably from 10 minutes to 12 hours. The reaction temperature is generally from -10 to 200°C, preferably from 0 to 120°C. The product (IX) can be used in the

next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, for example, through recrystallization, distillation, chromatography or the like.

Compound (VII) (where R^9 represents a hydrocarbon group) can be obtained by reacting compound (VI) and an ester derivative of the formula $R^3CH_2COOR^9$ (where R^3 and R^9 are as defined above) in the presence of a base. For the "hydrocarbon group" to be represented by R^9, for example, referred to is the above-mentioned "hydrocarbon group". Of the examples of the hydrocarbon group as mentioned above, R^9 is preferably a lower alkyl group (e.g., a C_{1-6} alkyl group, such as methyl, ethyl, isopropyl, etc.) or an optionally substituted benzyl group. The "optionally substituted benzyl group" may have one to three substituents, such as halogen atoms, C_{1-3} alkyl groups, etc., at any substitutable positions in the benzyl group. Concretely, it includes, for example, benzyl, p-chlorobenzyl, p-methylbenzyl, etc.

[0053]

The ester derivative is used in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 2.0 mols per mol of compound (VI). The base includes, for example, inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium

hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 2.0 mols per mol of compound (VI). The reaction is advantageously conducted in the presence of a solvent inert to the reaction. The solvent is not specifically defined so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; ketones such as acetone, methyl ethyl ketone, etc.; sulfoxides such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 30 minutes to 48 hours, preferably from 30 minutes to 5 hours. The reaction temperature is generally from -20 to 200°C, preferably from -10 to 150°C. The product (VII) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, for example, through recrystallization, distillation, chromatography or the like.

[0054]

Compound (VII) can also be produced by catalytically reducing compound (VIII) in a hydrogen

atmosphere in the presence of various catalysts. The catalysts usable for the reduction include, for example, platinum oxide, platinum on activated carbon, palladium on activated carbon, palladium on barium sulfate, nickel, copper-chromium oxide, rhodium, cobalt, ruthenium, etc. The amount of the catalyst to be used may be approximately from 5 to 1000% by weight, preferably approximately from 5 to 300% by weight relative to compound (VIII). The reaction is advantageously conducted in a solvent inert to the reaction. The solvent is not specifically defined so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; saturated hydrocarbons such as cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; organic acids such as formic acid, acetic acid, etc.; water, etc. Mixed solvents comprising them are also preferably used. The reaction time varies, depending on the activity of the catalyst used and the amount thereof. The reaction time is generally from 30 minutes to 24 hours, preferably from 30 minutes to 6 hours. The reaction temperature is generally from 0 to 120°C, preferably from 20 to 80°C. The pressure for the reaction is generally from 1 to 100 atmospheres. Additives (promoters) that enhance the activity of the catalyst used can be added to the reaction system. Acidic additives advantageously usable for the purpose include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, perchloric acid, hydrobromic acid, phosphoric acid, etc.; organic acids such as acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid, 10-

camphorsulfonic acid, etc. Basic additives are also advantageously usable and include, for example, sodium hydroxide, potassium hydroxide, etc. The product (VII) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0055]

Compound (V) can be produced by catalytically reducing compound (IV) or compound (IX) in a hydrogen atmosphere in the same manner as in the reduction to produce compound (VII).

Compound (V) can also be produced by hydrolyzing the ester moiety of compound (VII) with an acid or a base. For the acid hydrolysis, generally used are mineral acids such as hydrochloric acid, sulfuric acid, etc.; Lewis acids such as boron trichloride, boron trifluoride, etc.; a combination of a Lewis acid and a thiol or sulfide; organic acids such as trifluoroacetic acid, p-toluenesulfonic acid, etc. For the alkali hydrolysis, generally used are metal hydroxides such as sodium hydroxide, potassium hydroxide, barium hydroxide, etc.; metal carbonates such as sodium carbonate, potassium carbonate, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.; organic bases such as triethylamine, imidazole, formamidine, etc. These acids and bases are used in an amount of approximately from 0.5 to 10 mols, preferably approximately from 0.5 to 3.0 mols per mol of compound (VII). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. The solvent is not specifically defined so

far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; aromatic hydrocarbons such as benzene, toluene, etc.; saturated hydrocarbons such as cyclohexane, hexane, etc.; organic acids such as formic acid, acetic acid, etc.; ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; ketones such as acetone, methylethylketone, etc.; sulfoxides such as dimethylsulfoxide, etc.; water, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 10 minutes to 60 hours, preferably from 10 minutes to 12 hours. The reaction temperature is generally from -10 to 200°C, preferably from 0 to 120°C. The product (V) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0056]

Compound (XIV) can be produced from compound (XIII) and an aldehyde derivative of the formula R^4CHO (where R^4 is as defined above), through aldol condensation in the presence of a base. This is obtained as a single E-form or Z-form configurational isomer or as a mixture of such E- and Z-isomers. The aldehyde derivative is used in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 2.0 mols per mol of compound

(XIII). The base includes, for example, inorganic bases such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. These bases are used in an amount of approximately from 1.0 to 5.0 mols, preferably from 1.0 to 2.5 mols per mol of compound (XIII). The reaction is advantageously conducted in a solvent inert thereto. The solvent is not specifically defined so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 30 minutes to 48 hours, preferably from 30 minutes to 5 hours. The reaction temperature is generally from -78 to 200°C, preferably from -10 to 150°C. The aldol intermediate to be obtained in the presence of a base such as lithium diisopropylamide or the like can be dehydrated at room

temperature or under heat in the presence of an acid catalyst such as p-toluenesulfonic acid or the like to give the product. The product (XIV) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0057]

Compound (X) can be produced by a per se known method of cyclization of compound (V) or compound (XIV). For example, the cyclization can be conducted by a method of heating the compound, or a method of treating the compound with an acidic substance, or a method of first reacting the compound with a halogenating agent followed by cyclizing it in the presence of a Lewis acid, or methods analogous thereto.

The cyclization under heat is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. The solvent is not specifically defined so far as the reaction advances therein. Preferably, it includes, for example, high-boiling-point hydrocarbons such as 1,2,3,4-tetrahydronaphthalene, etc.; high-boiling-point ethers such as diphenyl ether, diethyleneglycol dimethyl ether, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 10 minutes to 24 hours, preferably from 10 minutes to 10 hours. The reaction temperature is generally from 100 to 300°C, preferably from 100 to 200°C.

The acidic substance for the cyclization includes, for example, phosphorus oxychloride, phosphorus pentoxide, phosphorus trioxide, thionyl chloride,

hydrochloric acid, sulfuric acid, polyphosphoric acid, p-toluenesulfonic acid, etc. The acidic substance is used in an amount of approximately from 0.5 to 100 mols, preferably approximately from 5.0 to 20 mols per mol of compound (V) or (XIV). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. The solvent is not specifically defined so far as the reaction advances therein. Preferably, it includes, for example, aromatic hydrocarbons such as benzene, toluene, etc.; saturated hydrocarbons such as cyclohexane, hexane, etc.; ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; acid anhydrides such as acetic anhydride, etc.; sulfoxides, such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 30 minutes to 12 hours, preferably from 30 minutes to 6 hours. The reaction temperature is generally from 0 to 200°C, preferably from 0 to 150°C. [0058]

In the method of reacting compound (V) with a halogenating agent followed by cyclizing it in the presence of a Lewis acid, the halogenating agent to be used includes, for example, thionyl halides such as thionyl chloride, thionyl bromide, etc.; phosphoryl halides such as phosphoryl chloride, phosphoryl bromide, etc.; phosphorus halides such as phosphorus pentachloride, phosphorus trichloride, phosphorus pentabromide, phosphorus tribromide, etc.; oxalyl halides such as oxalyl chloride, etc.; phosgene, etc. The halogenating agent is used in an amount of approximately from 1.0 to 30 mols, preferably

approximately from 1.0 to 10 mols per mol of compound (V). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. The solvent is not specifically defined so far as the reaction advances therein. Preferably, it includes, for example, aromatic hydrocarbons such as benzene, toluene, etc.; saturated hydrocarbons such as cyclohexane, hexane, etc.; ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 10 minutes to 12 hours, preferably from 10 minutes to 5 hours. The reaction temperature is generally from -10 to 200°C, preferably from -10 to 120°C. The product can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like. The Lewis acid to be used in the next cyclization includes, for example, anhydrous aluminium chloride, anhydrous zinc chloride, anhydrous iron chloride, etc. The Lewis acid is used in an amount of approximately from 0.1 to 20 mols, preferably approximately from 0.2 to 5.0 mols per mol of compound (V). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. The solvent is not specifically defined so far as the reaction advances therein. Preferably, it includes, for example, aromatic hydrocarbons such as benzene, toluene, etc.;

halogenated hydrocarbons such as monochlorobenzene, o-dichlorobenzene, 1,2,4-trichlorobenzene, dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 30 minutes to 12 hours, preferably from 30 minutes to 6 hours. The reaction temperature is generally from -20 to 200°C, preferably from -5 to 120°C. The product (X) obtained through the cyclization can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0059]

Compound (XII) can be produced by reacting a carbanion, which is formed by the treatment of acetonitrile with a base, with compound (X) to give compound (XI) followed by dehydrating the resulting compound (XI). Compound (XII) is obtained as a single E-form or Z-form configurational isomer or as a mixture of such E- and Z-isomers. Acetonitrile is used in an amount of approximately from 1.0 to 3.0 mols, preferably approximately from 1.0 to 1.3 mols per mol of compound (X). The base includes, for example, alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. These bases are used in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 1.5 mols per mol of compound (X). The reaction is advantageously conducted in the presence of a solvent inert to the

reaction. The solvent is not specifically defined so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 30 minutes to 48 hours, preferably from 30 minutes to 5 hours. The reaction temperature is generally from -78 to 100°C, preferably from -78 to 50°C. The product obtained can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0060]

The catalyst to be used for the dehydration includes, for example, acidic catalysts such as hydrochloric acid, sulfuric acid, phosphoric acid, potassium hydrogensulfate, oxalic acid, p-toluenesulfonic acid, 10-camphorsulfonic acid, boron trifluoride-ether complex, etc.; basic catalysts such as sodium hydroxide, potassium hydroxide, etc. If desired, a dehydrating agent such as N,N'-dicyclohexylcarbodiimide or the like as well as alumina, sodium dioxide, phosphorus oxychloride, thionyl chloride, methanesulfonyl chloride, etc. can also be used. The reaction is advantageously conducted in either the absence of a solvent or the presence of a

solvent inert to the reaction. The solvent is not specifically defined so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; sulfoxides such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 30 minutes to 24 hours, preferably from 30 minutes to 5 hours. The reaction temperature is generally from 0 to 200°C, preferably from 0 to 150°C.

[0061]

Compound (XII) can also be produced by reacting a phosphonate-carbanion, which is produced by the treatment of a trialkyl phosphonoacetate with a base, with compound (X). This is obtained as a single E-form or Z-form configurational isomer or as a mixture of such E- and Z-isomers. The trialkyl phosphonoacetate includes, for example, diethyl cyanomethylphosphonate, etc. One mol of compound (X) is reacted with approximately from 1.0 to 3.0 mols, preferably approximately from 1.0 to 1.5 mols of a trialkyl phosphonoacetate. The base includes, for example, alkali metal hydrides such as sodium hydride, potassium hydride, etc., metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 1.5 mols per mol of compound (X). The reaction is advantageously conducted in a solvent inert thereto. The solvent is not specifically defined so far as the reaction

advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; sulfoxides such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 1 hour to 50 hours, preferably from 1 hour to 10 hours. The reaction temperature is generally from -78 to 200°C, preferably from 0 to 150°C. The mixture of isomers of compound (XII) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0062]

The extension of the side carbon chain in compound (XII), if desired, can be conducted by means of any known carbon chain-extending reaction. As one example for the extension, the cyano-group bonding to the side carbon chain is hydrolyzed under alkaline or acidic conditions to convert it into a carboxyl group, which is then esterified, reduced to an alcohol, and thereafter halogenated and again cyanated.

Compound (XV) can be produced by reducing compound (XII). The reducing agent usable for this includes, for example, metal hydrides such as aluminium hydride, diisobutyl aluminium hydride, etc.; metal hydride complexes such as lithium aluminium hydride, sodium borohydride, etc. As the hydrogenation catalyst, for example, usable are Raney nickel, Raney cobalt, etc. Regarding the amount of the reducing agent, the metal

hydride is used in an amount of approximately from 1.0 to 10 mols, preferably approximately from 1.0 to 3.0 mols per mol of compound (XII) while the metal hydride complex is used in an amount of approximately from 1.0 to 10 mols, preferably from 1.0 to 3.0 mols per mol of compound (XII). For the hydrogenation, a catalyst such as Raney nickel, Raney cobalt or the like is used in an amount of approximately from 10 to 1000% by weight, preferably approximately from 80 to 300% by weight relative to compound (XII). The reaction is advantageously conducted in a solvent inert thereto. The solvent is not specifically defined so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; organic acids such as formic acid, acetic acid, etc. Mixed solvents comprising them are also preferably used. Where Raney nickel or Raney cobalt catalyst is used, amines such as ammonia, etc. may be added to the reaction system in order to prevent any possible side reactions. The reaction time varies, depending on the activity of the catalyst and the amount thereof used, and is generally from 1 hour to 100 hours, preferably from 1 hour to 50 hours. The reaction temperature is generally from 0 to 120°C, preferably from 20 to 80°C. Where Raney nickel, Raney cobalt or the like catalyst is used, the hydrogen pressure shall be generally from 1 to 100 atmospheres. The product (XV) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation,

such as, through recrystallization, distillation, chromatography or the like.

[0063]

Compound (XVI) with m = 2 or 3 can be produced by isomerizing compound (XV) with acids. Preferred examples of the acid catalyst to be used include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid, phosphoric acid, etc.; organic acids such as acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid, 10-camphorsulfonic acid, etc.; boron trifluoride-ether complex, etc. The acid catalyst is used in an amount of approximately from 0.01 to 10 mols, preferably approximately from 0.01 to 5.0 mols per mol of compound (XV). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. The solvent is not specifically defined so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; sulfoxides such as dimethylsulfoxide, etc.; water, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 10 minutes to 12 hours, preferably from 10 minutes to 2 hours. The reaction temperature is generally from -10 to 200°C, preferably from -10 to 100°C. The product (XVI) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture

by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

Compound (XVI) with m = 1 can be produced by treating compound (X) with trimethylsilylcyanide in the presence of a Lewis acid, then treating the resulting intermediate with an acid to remove its trimethylsilyloxy group and thereafter reducing it at its cyano group. The Lewis acid includes, for example, zinc iodide, anhydrous aluminium chloride, anhydrous zinc chloride, anhydrous iron chloride, etc. The Lewis acid catalyst is used in an amount of approximately from 0.01 to 10 mols, preferably approximately from 0.01 to 1.0 mol per mol of compound (X). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 10 minutes to 12 hours, preferably from 30 minutes to 3 hours. The reaction temperature is generally from -10 to 200°C, preferably from -10 to 100°C. The intermediate can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like. Next, the intermediate is treated with an acid. Preferably, the acid includes, for example, inorganic acids such as

hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid, phosphoric acid, etc.; organic acids such as acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid, 10-camphorsulfonic acid, etc.; boron trifluoride-ether complex, etc. The acid is used in an amount of approximately from 1 to 100 mols, preferably approximately from 1 to 10 mols per mol of compound (X). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. The solvent is not specifically defined so far as the reaction advances therein. Preferably, it includes, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; sulfoxides such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 30 minutes to 12 hours, preferably from 30 minutes to 5 hours. The reaction temperature is generally from 0 to 200°C, preferably from 20 to 150°C. The reduction of the cyano group in the resulting intermediate can be conducted under the same conditions as those for the production of compound (XV) from compound (XII). The product (XVI) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0064]

Compound (XVII) can be produced by reacting

compound (XVI) with a carboxylic acid or with its salt or reactive derivative. The carboxylic acid includes, for example, compounds of the formula R^1-COOH (where R^1 is as defined above). The reactive derivatives of the carboxylic acid include, for example, acid halides (e.g., acid chlorides, acid bromides, etc.), acid amides (e.g., acid amides with pyrazole, imidazole, benzotriazole, etc.), mixed acid anhydrides (e.g., mixed mono-C_{1-4} alkyl carbonate anhydrides derived from monomethyl carbonate, monoethyl carbonate, monoisopropyl carbonate, mono-tert-butyl carbonate; mixed mono-C_{7-10} aralkyl carbonate anhydrides derived from monobenzyl carbonate, mono(p-nitrobenzyl) carbonate, monoallyl carbonate; mixed C_{1-6} aliphatic carboxylic acid anhydrides derived from acetic acid, cyanoacetic acid, propionic acid, butyric acid, isobutyric acid, valeric acid, isovaleric acid, pivalic acid, trifluoroacetic acid, trichloroacetic acid, acetacetic acid; mixed C_{7-11} aromatic carboxylic acid anhydrides derived from benzoic acid, p-toluic acid, p-chlorobenzoic acid; mixed organic sulfonic acid anhydrides derived from methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.), acid azides, active esters (e.g., diethoxyphosphates, diphenoxyphosphates, p-nitrophenyl esters, 2,4-dinitrophenyl esters, cyanomethyl esters, pentachlorophenyl esters, esters with N-hydroxysuccinimide, esters with N-hydroxyphthalimide, esters with 1-hydroxybenzotriazole, esters with 6-chloro-1-hydroxybenzotriazole, esters with 1-hydroxy-1H-2-pyridone, etc.), active thioesters (e.g., 2-pyridyl thioesters, 2-benzothiazolyl thioesters, etc.), etc.

[0065]

In place of using the reactive derivative, the carboxylic acid or its salt may be directly reacted

with compound (XVI) in the presence of a suitable condensing agent. The condensing agent includes, for example, N,N'-di-substituted carbodiimides such as N,N'-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (WSC) hydrochloride, etc.; azolides such as N,N'-carbonyldiimidazole, etc.; dehydrating agents such as N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, phosphorus oxychloride, alkoxyacetylenes, etc.; 2-halogenopyridinium salts such as 2-chloromethylpyridinium iodide, 2-fluoro-1-methylpyridinium iodide, etc. It is believed that the reaction with the condensing agent may advance via the reactive derivative of the carboxylic acid used. The carboxylic acid of R^1-COOH (where R^1 is as defined above) or its reactive derivative is used generally in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 2.0 mols per mol of compound (XVI). The reaction is advantageously conducted in a solvent inert to the reaction. The solvent is not specifically defined so far as the reaction advances therein. Preferably, it includes, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. Where acid halides are used as the reactive derivatives of carboxylic acids, the reaction may be conducted in the presence of a de-acidifying agent in order to remove the released hydrogen halide from the reaction system. The de-acidifying agent includes, for example, inorganic bases

such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc. It is desirable that such a de-acidifying agent is previously added to the reaction system. The reaction time varies, depending on the reagents and the solvents used, and is generally from 30 minutes to 24 hours, preferably from 30 minutes to 4 hours. The reaction temperature is generally from 0 to 100°C, preferably from 0 to 70°C.

[0066]

Compound (XVII) can also be produced by adding to compound (XV) a carboxylic acid of R^1-COOH (where R^1 is as defined above) or its reactive derivative, stirring them under acidic conditions for from 5 minutes to 3 hours, preferably from 10 minutes to 1 hour, at from 0 to 100°C, preferably from 0 to 70°C, and thereafter adding a de-acidifying agent such as that mentioned above to the reaction system to thereby make the resulting intermediate acylated. The process is accompanied by isomerization of the reaction system to give compound (XVII). The carboxylic acid or its reactive derivative is used generally in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 2.0 mols per mol of compound (XV). The reaction is advantageously conducted in a solvent inert to the reaction. The solvent is not specifically defined so far as the reaction advances therein. Preferably, it includes, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, etc.; amides such as N,N-

dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. The product (XVII) thus obtained can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0067]

To obtain compound (XVII) wherein R^2 is an alkyl group, the acylated compound as obtained in the above is alkylated with a corresponding alkylating agent (e.g., alkyl halides, sulfonates with alcohols) in the presence of a base. The alkylating agent is used in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 2.0 mols per mol of compound (XVII) to be alkylated therewith. The base includes, for example, inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is

used in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 2.0 mols per mol of compound (XVII). The reaction is advantageously conducted in a solvent inert to the reaction. The solvent is not specifically defined so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 30 minutes to 48 hours, preferably from 30 minutes to 6 hours. The reaction temperature is generally from -20 to 200°C, preferably from -10 to 150°C. The product (XVII) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0068]

To obtain compound (XVII) in which the double-bond moiety has been reduced, the double-bond moiety in compound (XVII) is catalytically reduced under the same conditions as those for the production of compound (VII) from compound (VIII).

Compound (XVIII) can be produced by removing the protective group for the hydroxyl group in compound

(XVII). The de-protecting step shall be conducted by ordinary known means. For example, referred to is the disclosure in the chapter "Protection for Phenols and Catechols" in "Protective Groups in Organic Synthesis" by T. W. Green (2nd Ed., 1991).

Compound (XIX) can be produced by reacting compound (XVIII) with a corresponding alkylating agent (e.g., alkyl halides, sulfonates with alcohols, etc.) in the presence of a base. The alkylating agent is used in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 2.0 mols per mol of compound (XVIII). The base includes, for example, inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 2.0 mols per mol of compound (XVIII). The reaction is advantageously conducted in a solvent inert to the reaction. The solvent is not specifically defined so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide,

etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 30 minutes to 48 hours, preferably from 1 to 24 hours. The reaction temperature is generally from -20 to 200°C, preferably from 0 to 150°C. The product (XIX) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0069]

Compound (XX) can be produced by reacting compound (XVIII) with a corresponding α-haloketone in the presence of a base. The α-haloketone is used in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 2.0 mols per mol of compound (XVIII). The base includes, for example, inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of

approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 2.0 mols per mol of compound (XVIII). The reaction is advantageously conducted in a solvent inert to the reaction. The solvent is not specifically defined so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; ketones such as acetone, methyl ethyl ketone, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 30 minutes to 48 hours, preferably from 1 to 24 hours. The reaction temperature is generally from -20 to 200°C, preferably from 0 to 150°C. The product (XX) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0070]

Compound (XXI) can be produced by reacting compound (XVIII) with a corresponding alkylating agent (e.g., substituted acetylenealkyl halides, sulfonates with substituted acetyleue alcohols, etc.) in the presence of a base. The alkylating agent is used in an amount of approximately from 1.0 to 20 mols, preferably approximately from 1.0 to 10 mols per mol of compound

(XVIII). The base includes, for example, inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 2.0 mols per mol of compound (XVIII). The reaction is advantageously conducted in a solvent inert to the reaction. The solvent is not specifically defined so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 30 minutes to 48 hours, preferably from 1 to 24 hours. The reaction temperature is generally from -20 to 200°C, preferably from 0 to 150°C. The product (XXI) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated

from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0071]

Compound (I) can be produced by per se known cyclization of compound (XIX), (XX) or (XXI). For example, the cyclization can be conducted by a method of heating the compound, or a method of treating the compound with an acidic substance, or a method of treating the compound with a basic substance, or methods analogous thereto.

The cyclization under heat is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. The solvent is not specifically defined so far as the reaction advances therein. Preferably, it includes, for example, high-boiling-point hydrocarbons such as 1,2,3,4-tetrahydronaphthalene, bromobenzene etc.; high-boiling-point ethers such as diphenyl ether, diethyleneglycol dimethyl ether, etc.; N,N-dimethylaniline, N,N-diethylaniline, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 10 minutes to 24 hours, preferably from 10 minutes to 10 hours. The reaction temperature is generally from 100 to 300°C, preferably from 150 to 250°C.

The acidic substance to be used in the cyclization includes, for example, phosphorus oxychloride, phosphorus pentoxide, phosphorus trioxide, thionyl chloride, hydrobromic acid, hydrochloric acid, sulfuric acid, phosphoric acid, polyphosphoric acid, p-toluenesulfonic acid, etc. The acidic substance is used in an amount of approximately from 0.5 to 100 mols, preferably approximately from 5.0 to 20 mols per mol of compound (XIX), (XX) or (XXI). The reaction is

advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. The solvent is not specifically defined so far as the reaction advances therein. Preferably, it includes, for example, aromatic hydrocarbons such as benzene, toluene, etc.; saturated hydrocarbons such as cyclohexane, hexane, etc.; ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; acid anhydrides such as acetic anhydride, etc.; sulfoxides, such as dimethylsulfoxide, etc.; water, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 30 minutes to 12 hours, preferably from 30 minutes to 6 hours. The reaction temperature is generally from 0 to 200°C, preferably from 0 to 150°C.

[0072]

The basic substance to be used in the cyclization includes, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, etc. The basic substance is used in an amount of approximately from 0.5 to 100 mols, preferably approximately from 5.0 to 20 mols per mol of compound (XIX), (XX) or (XXI). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. The solvent is not specifically defined so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ketones such as acetone, methyl ethyl ketone, etc.; water, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 30 minutes to 12 hours,

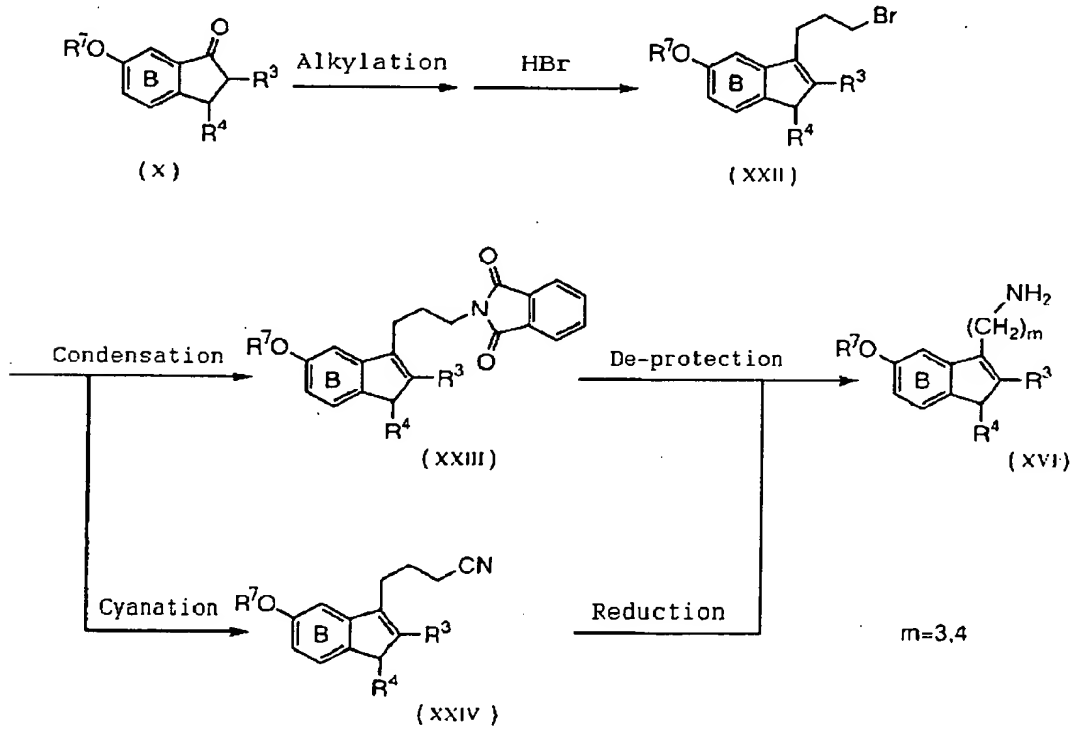
preferably from 30 minutes to 6 hours. The reaction temperature is generally from 0 to 200°C, preferably from 0 to 150°C.

The product (I) obtained through the cyclization can be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

To obtain compound (I) in which the double-bond moiety has been reduced, the double-bond moiety in compound (I) is catalytically reduced under the same conditions as those for the production of compound (VII) from compound (VIII).

[0073]

Reaction Process 2:



[0074]

Compound (XXII) can be produced by alkylating compound (X) followed by treating it with hydrobromic

acid. For the alkylation, a Grignard reagent to be prepared from cyclopropyl bromide and magnesium is diluted with an inert solvent and then applied to compound (X). The production of the Grignard reagent from cyclopropyl bromide may be conducted by known methods. Magnesium is used in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 1.5 mols, per mol of cyclopropyl bromide. The reaction is advantageously conducted in a solvent inert to the reaction. The solvent is not specifically defined so far as the reaction advances therein. Preferably, it includes, for example, aromatic hydrocarbons such as benzene, toluene, etc.; saturated hydrocarbons such as cyclohexane, hexane, etc.; ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 10 minutes to 10 hours, preferably from 15 minutes to 3 hours. The reaction temperature is generally from 0 to 150°C, preferably from 40 to 80°C. A small amount of iodine may be present in the reaction system. The Grignard reagent thus produced is left at room temperature to complete the reaction. Then, after removing the solvent through distillation or without removing it, the Grignard reagent is diluted with a solvent added thereto, and compound (X) is dropwise added to and reacted with the reagent. Compound (X) is used in an amount of approximately from 0.4 to 3.0 mols, preferably approximately from 0.4 to 1.0 mol per mol of the Grignard reagent. The solvent to be used for diluting the Grignard reagent is not specifically defined so far as the intended reaction advances therein. It includes, for example, aromatic hydrocarbons such as benzene, toluene, etc.; saturated hydrocarbons such as cyclohexane, hexane, etc.;

halogenated hydrocarbons such as chlorotoluene, etc.; ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc. Mixed solvents comprising them are also preferably used. The amount of the solvent to be used for the dilution may be approximately from 1.0 to 30 times by volume, preferably approximately from 1.0 to 15 times by volume of the Grignard reagent. The reaction time is generally from 10 minutes to 10 hours, preferably from 15 minutes to 3 hours. The reaction temperature is generally from 0 to 150°C, preferably from 40 to 100°C. The product can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like. The amount of the hydrobromic acid to be used is approximately from 1.0 to 30 mols, preferably approximately from 1.0 to 5.0 mols per mol of compound (X). The reaction is advantageously conducted in a solvent inert to the reaction. The solvent is not specifically defined so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; organic acids such as formic acid, acetic acid, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; sulfoxides such as dimethylsulfoxide, etc.; water, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 1 to 60 hours, preferably from 1 to 15 hours. The reaction temperature is generally from 0 to 200°C, preferably from 0 to 80°C. The product (XXII) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction

mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0075]

Compound (XXIII) can be produced by reacting compound (XXII) with potassium phthalimide. Potassium phthalimide is used in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 1.5 mols per mol of compound (XXII). The condensation of compound (XXII) with potassium phthalimide is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction and optionally in the presence of a base. The base includes, for example, inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The amount of the base to be used is approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 2.0 mols per mol of compound (XXII). Preferably, the solvent includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons

such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 30 minutes to 20 hours, preferably from 30 minutes to 8 hours. The reaction temperature is generally from 0 to 150°C, preferably from 20 to 80°C. The product (XXIII) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0076]

Compound (XXIV) can be produced by reacting compound (XXII) with a cyano compound. The cyano compound includes sodium cyanide, potassium cyanide and a mixture of these. It may be produced in the reaction system by reacting hydrogen cyanide with an alkali metal salt such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate or the like. The cyano compound is used in an amount of approximately from 0.8 to 10 mols, preferably approximately from 1.0 to 2.0 mols per mol of compound (XXII). The reaction is advantageously conducted in a solvent inert thereto. The solvent is not specifically defined so far as the reaction advances therein. Preferably, it includes, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane,

chlorobenzene, ortho-dichlorobenzene, etc.; sulfoxides such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. A combination of water and a water-insoluble or hardly water-soluble organic solvent such as that selected from the above can also be employed in the presence of a phase-transfer catalyst. The phase-transfer catalyst includes, for example, quaternary ammonium salts such as tetrabutylammonium bromide, benzyltriethylammonium chloride, etc.; and quaternary phosphonium salts. The amount of the phase-transfer catalyst, if used, may be approximately from 0.001 to 10 mols, preferably approximately from 0.005 to 0.5 mols per mol of compound (XXII). The reaction time is generally from 30 minutes to 20 hours, preferably from 30 minutes to 8 hours. The reaction temperature is generally from 0 to 200°C, preferably from 20 to 150°C. The product (XXIV) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0077]

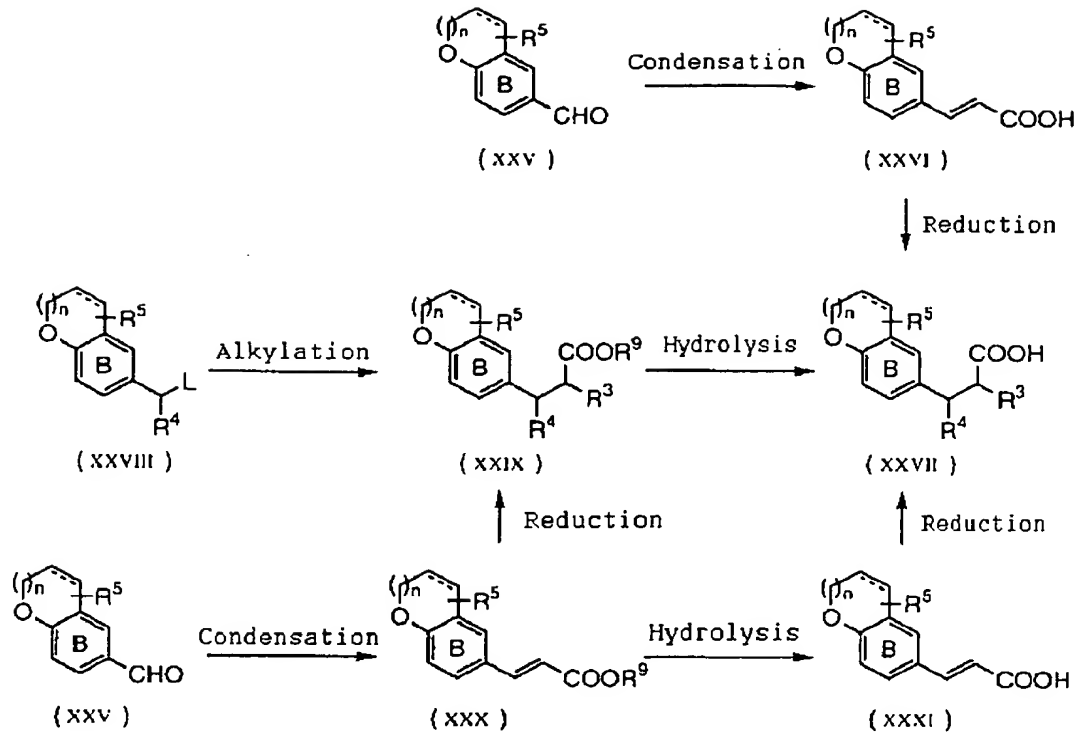
Compound (XVI) can be produced by decomposing the imido group in compound (XXIII). For this, in general, 1 mol of compound (XXIII) is treated with approximately from 1.0 to 20 mols, preferably approximately from 1.0 to 5.0 mols of amines such as methylamine, ethylamine, etc., hydrazines such as hydrazine, phenylhydrazine, etc., alkali sulfides such as sodium sulfide, potassium sulfide, etc., mineral acids such as hydrochloric acid, sulfuric acid, etc. The reaction is advantageously conducted in a solvent inert thereto. The solvent is not specifically defined so far as the reaction

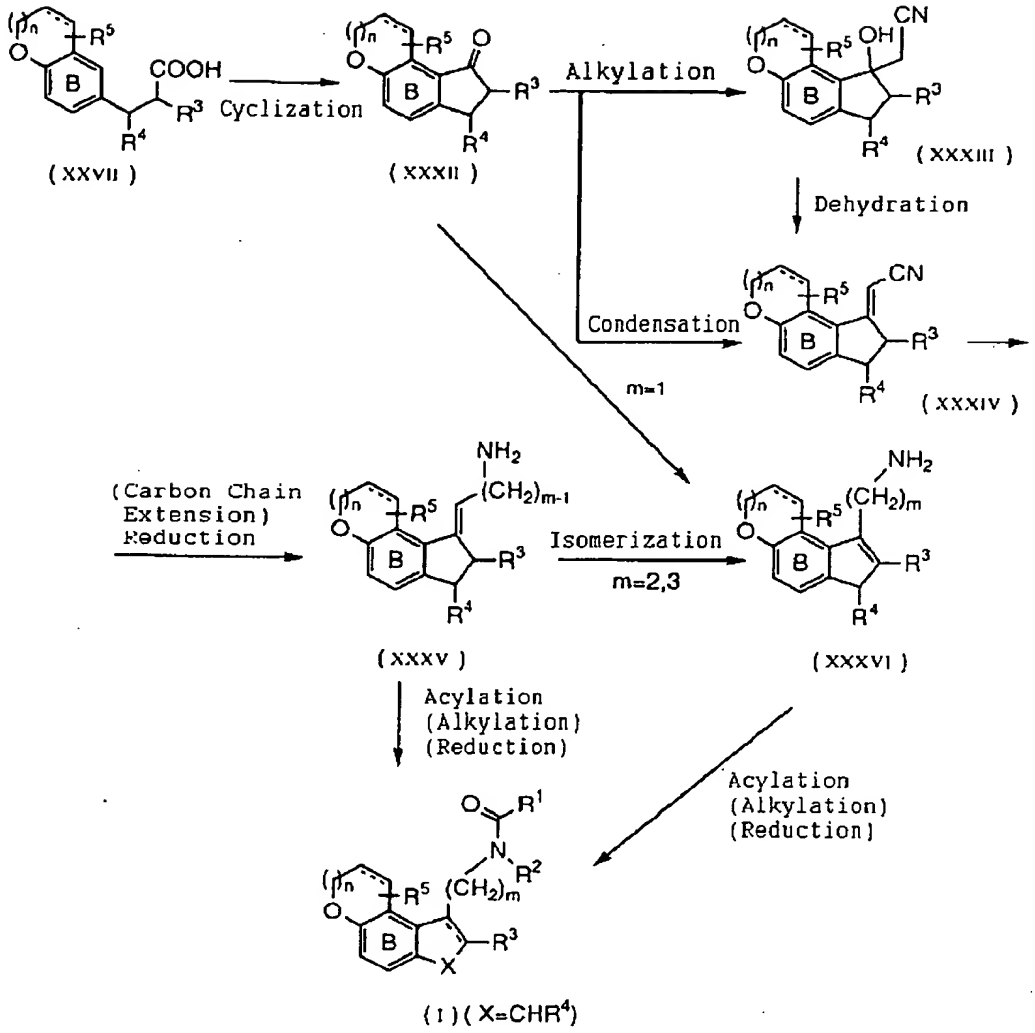
advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; sulfoxides such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 30 minutes to 12 hours, preferably from 30 minutes to 5 hours. The reaction temperature is generally from 0 to 200°C, preferably from 20 to 100°C. The product (XVI) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

Compound (XVI) can also be produced by reducing the cyano group in compound (XXIV) in the same manner as in the production of compound (XV) from compound (XII).

[0078]

Reaction Process 3:


Condensation
Reduction
Alkylation
Hydrolysis
Reduction
Reduction
Condensation
Hydrolysis
(XXV)
(XXVI)
(XXVIII)
(XXIX)
(XXVII)
(XXV)
(XXX)
(XXXI)



[0079]

Compound (XXV) can be produced using per se known methods, for example, using the methods described in J. Org. Chem., Vol. 49, p. 409 (1984) and J. Indian Chem. Soc., Vol. 36, p. 76 (1959), or methods analogous thereto.

Compound (XXVIII) (wherein L represents a removing group such as a halogen atom, an alkylsulfonyl group, an alkylsulfonyloxy group, an arylsulfonyloxy group, etc.) can be produced using per se known methods, for example, using the methods described in J. Chem. Soc.,

p. 2455 (1956) and ibid., p. 4665 (1958), or methods analogous thereto.

[0080]

The halogen atom to be represented by L includes, for example, fluorine, chlorine, bromine, iodine, etc. The alkylsulfonyl group to be represented by L includes, for example, a C_{1-5} alkylsulfonyl group (e.g., methanesulfonyl, ethanesulfonyl, etc.), etc. The alkylsulfonyloxy group to be represented by L includes, for example, an optionally halogenated C_{1-5} alkylsulfonyloxy group (e.g., methanesulfonyloxy, ethanesulfonyloxy, trichloromethanesulfonyloxy, etc.), etc. The arylsulfonyloxy group to be represented by L includes, for example, an optionally substituted benzenesulfonyloxy group (e.g., p-toluenesulfonyloxy, benzenesulfonyloxy, etc.), etc.

As the compounds in the above-mentioned reaction schemes are commercial products, if available, they can be directly used.

Compound (XXVI) can be produced from compound (XXV) and malonic acid through the Knoevenagel condensation thereof in the presence of a base, in the same manner as in the production of compound (IV) from compound (III) mentioned hereinabove. One mol of compound (XXV) is reacted with approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 2.0 mols of malonic acid. The base includes, for example, inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc. The base is used in an amount of approximately from 0.1 to 5.0 mols, preferably

approximately from 0.1 to 1.0 mol per mol of compound (XXV). The reaction is advantageously conducted in a solvent inert thereto. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; organic acids such as formic acid, acetic acid, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc. Mixed solvents comprising them are also preferably used. The reaction time varies, depending on the reagents and solvents used, and is generally from 30 minutes to 24 hours, preferably from 30 minutes to 4 hours. The reaction temperature is generally from 0 to 100°C, preferably from 0 to 70°C. The product (XXVI) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0081]

Compound (XXX) can be obtained by reacting a phosphonate-carbanion, which is produced by the treatment of a dialkyl alkylphosphonate with a base, with compound (XXV), in the same manner as in the production of compound (VIII) from compound (III) mentioned hereinabove. This is obtained as a single E-form or Z-form configurational isomer or as a mixture of such E- and Z-isomers. As mentioned hereinabove, the dialkyl alkylphosphonate includes, for example, ethyl diethylphosphonoacetate, etc. One mol of compound (XXV) is reacted with approximately from 1.0

to 3.0 mols, preferably approximately from 1.0 to 1.5 mols of a dialkyl alkylphosphonate. The base includes, for example, alkali metal hydrides such as sodium hydride, potassium hydride, etc., metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 1.5 mols, per mol of compound (XXV). The reaction is advantageously conducted in a solvent inert thereto. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; sulfoxides such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 1 hour to 50 hours, preferably from 1 hour to 10 hours. The reaction temperature is generally from -78 to 200°C, preferably from 0 to 150°C. The mixture of isomers of compound (XXX) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0082]

Compound (XXXI) can be produced by hydrolyzing the ester moiety of compound (XXX) with an acid or base, in the same manner as in the production of compound (IX)

from compound (VIII) mentioned hereinabove. For the acid hydrolysis, generally used are mineral acids such as hydrochloric acid, sulfuric acid, etc.; Lewis acids such as boron trichloride, boron trifluoride, etc.; a combination of a Lewis acid and a thiol or sulfide; organic acids such as trifluoroacetic acid, p-toluenesulfonic acid, etc. For the alkali hydrolysis, generally used are metal hydroxides such as sodium hydroxide, potassium hydroxide, barium hydroxide, etc.; metal carbonates such as sodium carbonate, potassium carbonate, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.; organic bases such as triethylamine, imidazole, formamidine, etc. These acids and bases are used in an amount of approximately from 0.5 to 10 mols, preferably approximately from 0.5 to 3.0 mols per mol of compound (XXX). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; aromatic hydrocarbons such as benzene, toluene, etc.; saturated hydrocarbons such as cyclohexane, hexane, etc.; organic acids such as formic acid, acetic acid, etc.; ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; ketones such as acetone, methyl ethyl ketone, etc.; sulfoxides such as dimethylsulfoxide, etc.; water, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 10 minutes to 60 hours, preferably from 10 minutes to

12 hours. The reaction temperature is generally from -10 to 200°C, preferably from 0 to 120°C. The product (XXXI) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0083]

Compound (XXIX) can be obtained by reacting compound (XXVIII) and an ester derivative of the formula $R^3CH_2COOR^9$ (where R^3 and R^9 are as defined above) in the presence of a base, in the same manner as in the production of compound (VII) from compound (VI) mentioned hereinabove. As the "hydrocarbon group" to be represented by R^9, for example, referred to is the above-mentioned "hydrocarbon group". Of the examples of the hydrocarbon group as mentioned above, R^9 is preferably a lower alkyl group (e.g., a C_{1-6} alkyl group, such as methyl, ethyl, isopropyl, etc.) or an optionally substituted benzyl group. The "optionally substituted benzyl group" may have one to three substituents, such as halogen atoms, C_{1-3} alkyl groups, etc., at any substitutable position in the benzyl group. Concretely, it includes, for example, benzyl, p-chlorobenzyl, p-methylbenzyl, etc.

The ester derivative is used in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 2.0 mols per mol of compound (XXVIII). The base includes, for example, inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-

dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 2.0 mols per mol of compound (XXVIII). The reaction is advantageously conducted in the presence of a solvent inert to the reaction. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; ketones such as acetone, methyl ethyl ketone, etc.; sulfoxides such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 30 minutes to 48 hours, preferably from 30 minutes to 5 hours. The reaction temperature is generally from -20 to 200°C, preferably from -10 to 150°C. The product (XXIX) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0084]

Compound (XXIX) can also be produced by catalytically reducing compound (XXX) in a hydrogen atmosphere in the presence of various catalysts, in the same manner as in the catalytic reduction of compound (VIII) into compound (VII) mentioned hereinabove. The catalysts usable for the reduction include, for example, platinum oxide, platinum on activated carbon palladium on activated carbon, palladium on barium sulfate nickel, copper-chromium oxide, rhodium, cobalt, ruthenium, etc. The amount of the catalyst to be used may be approximately from 5 to 1000% by weight, preferably approximately from 5 to 300% by weight relative to compound (XXX). The reaction is advantageously conducted in a solvent inert to the reaction. The solvent is not specifically defined so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; saturated hydrocarbons such as cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; organic acids such as formic acid, acetic acid, etc.; water, etc. Mixed solvents comprising them are also preferably used. The reaction time varies, depending on the activity of the catalyst and the amount thereof used. In general, it is from 30 minutes to 24 hours, preferably from 30 minutes to 6 hours. The reaction temperature is generally from 0 to 120°C, preferably from 20 to 80°C. The pressure for the reaction is generally from 1 to 100 atmospheres. Additives (promoters) that enhance the activity of the catalyst used can be added to the reaction system. Acidic additives advantageously usable for this purpose include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid,

perchloric acid, hydrobromic acid, phosphoric acid, etc.; organic acids such as acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid, 10-camphorsulfonic acid, etc. Basic additives are also advantageously usable and include, for example, sodium hydroxide, potassium hydroxide, etc. The product (XXIX) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0085]

Compound (XXVII) can be produced by catalytically reducing compound (XXVI) or compound (XXXI) in a hydrogen atmosphere in the same manner as in the catalytic reduction of compound (XXX) into compound (XXIX) or in the catalytic reduction of compound (IV) or compound (IX) into compound (V) mentioned hereinabove.

[0086]

Compound (XXVII) can also be produced by hydrolyzing the ester moiety of compound (XXIX) with an acid or base, in the same manner as in the production of compound (V) from compound (VII) mentioned hereinabove. For the acid hydrolysis, generally used are mineral acids such as hydrochloric acid, sulfuric acid, etc.; Lewis acids such as boron trichloride, boron trifluoride, etc.; a combination of a Lewis acid and a thiol or sulfide; organic acids such as trifluoroacetic acid, p-toluenesulfonic acid, etc. For the alkali hydrolysis, generally used are metal hydroxides such as sodium hydroxide, potassium

hydroxide, barium hydroxide, etc.; metal carbonates such as sodium carbonate, potassium carbonate, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.; organic bases such as triethylamine, imidazole, formamidine, etc. These acids and bases are used in an amount of approximately from 0.5 to 10 mols, preferably approximately from 0.5 to 3.0 mols per mol of compound (XXIX). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. The solvent is not specifically defined so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; aromatic hydrocarbons such as benzene, toluene, etc.; saturated hydrocarbons such as cyclohexane, hexane, etc.; organic acids such as formic acid, acetic acid, etc.; ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; ketones such as acetone, methyl ethyl ketone, etc.; sulfoxides such as dimethylsulfoxide, etc.; water, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 10 minutes to 60 hours, preferably from 10 minutes to 12 hours. The reaction temperature is generally from -10 to 200°C, preferably from 0 to 120°C. The product (XXVII) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography

or the like.

[0087]

Compound (XXXII) can be produced by per se known cyclization of compound (XXVII), in the same manner as in the cyclization of compound (V) into compound (X) mentioned hereinabove. For example, the cyclization can be conducted using a method of heating the compound, or a method of treating the compound with an acidic substance, or a method of first reacting the compound with a halogenating agent followed by cyclizing it in the presence of a Lewis acid, or methods analogous thereto.

The cyclization under heat is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, high-boiling-point hydrocarbons such as 1,2,3,4-tetrahydronaphthalene, etc.; high-boiling-point ethers such as diphenyl ether, diethyleneglycol dimethyl ether, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 10 minutes to 24 hours, preferably from 10 minutes to 10 hours. The reaction temperature is generally from 100 to 300°C, preferably from 100 to 200°C.

The acidic substance for use in the cyclization includes, for example, phosphorus oxychloride, phosphorus pentoxide, phosphorus trioxide, thionyl chloride, hydrochloric acid, sulfuric acid, polyphosphoric acid, p-toluenesulfonic acid, etc. The acidic substance is used in an amount of approximately from 0.5 to 100 mols, preferably approximately from 5.0 to 20 mols per mol of compound (XXVII). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the

reaction. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, aromatic hydrocarbons such as benzene, toluene, etc.; saturated hydrocarbons such as cyclohexane, hexane, etc.; ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; acid anhydrides such as acetic anhydride, etc.; sulfoxides, such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 30 minutes to 12 hours, preferably from 30 minutes to 6 hours. The reaction temperature is generally from 0 to 200°C, preferably from 0 to 150°C. [0088]

In the method of reacting compound (XXVII) with a halogenating agent followed by cyclizing it in the presence of a Lewis acid, the halogenating agent to be used includes, for example, thionyl halides such as thionyl chloride, thionyl bromide, etc.; phosphoryl halides such as phosphoryl chloride, phosphoryl bromide, etc.; phosphorus halides such as phosphorus pentachloride, phosphorus trichloride, phosphorus pentabromide, phosphorus tribromide, etc.; oxalyl halides such as oxalyl chloride, etc.; phosgene, etc. The halogenating agent is used in an amount of approximately from 1.0 to 30 mols, preferably approximately from 1.0 to 10 mols per mol of compound (XXVII). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, aromatic hydrocarbons such as benzene, toluene, etc.;

saturated hydrocarbons such as cyclohexane, hexane, etc.; ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 10 minutes to 12 hours, preferably from 10 minutes to 5 hours. The reaction temperature is generally from -10 to 200°C, preferably from -10 to 120°C. The product can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like. The Lewis acid to be used in the next cyclization includes, for example, anhydrous aluminium chloride, anhydrous zinc chloride, anhydrous iron chloride, etc. The Lewis acid is used in an amount of approximately from 0.1 to 20 mols, preferably approximately from 0.2 to 5.0 mols per mol of compound (XXVII). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, aromatic hydrocarbons such as benzene, toluene, etc.; halogenated hydrocarbons such as monochlorobenzene, o-dichlorobenzene, 1,2,4-trichlorobenzene, dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 30 minutes to 12 hours, preferably from 30 minutes to 6 hours. The reaction temperature is

generally from -20 to 200°C, preferably from -5 to 120°C. The product (XXXII) obtained through the cyclization can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

Compound (XXXIV) can be produced by reacting a carbanion, which is formed by the treatment of acetonitrile with a base, with compound (XXXII) to give compound (XXXIII) followed by dehydrating the resulting compound (XXXIII), in the same manner as in the production of compound (XII) from compound (X) mentioned hereinabove. Compound (XXXIV) is obtained as a single E-form or Z-form configurational isomer or as a mixture of such E- and Z-isomers. Acetonitrile is used in an amount of approximately from 1.0 to 3.0 mols, preferably approximately from 1.0 to 1.3 mols per mol of compound (XXXII). The base includes, for example, alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. These bases are used in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 1.5 mols per mol of compound (XXXII). The reaction is advantageously conducted in the presence of a solvent inert to the reaction. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.;

hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 30 minutes to 48 hours, preferably from 30 minutes to 5 hours. The reaction temperature is generally from -78 to 100°C, preferably from -78 to 50°C. The product obtained can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

The catalyst to be used for the dehydration includes, for example, acidic catalysts such as hydrochloric acid, sulfuric acid, phosphoric acid, potassium hydrogensulfate, oxalic acid, p-toluenesulfonic acid, 10-camphorsulfonic acid, boron trifluoride-ether complex, etc.; basic catalysts such as sodium hydroxide, potassium hydroxide, etc. If desired, a dehydrating agent such as N,N-cyclohexylcarbodiimide or the like as well as alumina, sodium dioxide, phosphorus oxychloride, thionyl chloride, methanesulfonyl chloride, etc. can also be used. The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as

benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; sulfoxides such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 30 minutes to 24 hours, preferably from 30 minutes to 5 hours. The reaction temperature is generally from 0 to 200°C, preferably from 0 to 150°C.

Compound (XXXIV) can also be produced by reacting a phosphonate-carbanion, which is produced by the treatment of a dialkyl alkylphosphonate with a base, with compound (XXXII), in the same manner as in the production of compound (XII) from compound (X) mentioned hereinabove. This is obtained as a single E-form or Z-form configurational isomer or as a mixture of such E- and Z-isomers. The dialkyl alkylphosphonate includes, for example, diethyl cyanomethylphosphonate, etc. One mol of compound (XXXII) is reacted with approximately from 1.0 to 3.0 mols, preferably approximately from 1.0 to 1.5 mols of a dialkyl alkylphosphonate. The base includes, for example, alkali metal hydrides such as sodium hydride, potassium hydride, etc., metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 1.5 mols per mol of compound (XXXII). The reaction is advantageously conducted in a solvent inert thereto. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane,

hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; sulfoxides such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 1 hour to 50 hours, preferably from 1 hour to 10 hours. The reaction temperature is generally from -78 to 200°C, preferably from 0 to 150°C. The mixture of isomers of compound (XXXIV) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

The extension of the side carbon chain in compound (XXXIV), if desired, can be conducted by any known carbon chain-extending reaction. As one example of a method of extension, the cyano group bonding to the side carbon chain is hydrolyzed under alkaline or acidic conditions to convert it into a carboxyl group, which is then esterified, reduced to an alcohol, and thereafter halogenated and again cyanated.

[0089]

Compound (XXXV) can be produced by reducing compound (XXXIV), in the same manner as in the production of compound (XV) from compound (XII) mentioned hereinabove. The reducing agent usable for this includes, for example, metal hydrides such as aluminium hydride, diisobutyl aluminium hydride, etc.; metal hydride complexes such as lithium aluminium hydride, sodium borohydride, etc. As the hydrogenation catalyst, for example, usable are Raney nickel, Raney cobalt, etc. Regarding the amount of the reducing agent, the metal hydride is used in an amount of approximately from 1.0 to 10 mols, preferably

approximately from 1.0 to 3.0 mols per mol of compound (XXXIV) while the metal hydride complex is used in an amount of approximately from 1.0 to 10 mols, preferably from 1.0 to 3.0 mols per mol of compound (XXXIV). For the hydrogenation, a catalyst such as Raney nickel, Raney cobalt or the like is used in an amount of approximately from 10 to 1000% by weight, preferably approximately from 80 to 300% by weight relative to compound (XXXIV). The reaction is advantageously conducted in a solvent inert thereto. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; organic acids such as formic acid, acetic acid, etc. Mixed solvents comprising them are also preferably used. Where a Raney nickel or Raney cobalt catalyst is used, amines such as ammonia, etc. may be added to the reaction system in order to prevent any possible side reactions. The reaction time varies, depending on the activity of the catalyst and the amount thereof used, and is generally from 1 hour to 100 hours, preferably from 1 hour to 50 hours. The reaction temperature is generally from 0 to 120°C, preferably from 20 to 80°C. Where Raney nickel, Raney cobalt or the like catalyst is used, the hydrogen pressure shall be generally from 1 to 100 atmospheres. The product (XXXV) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the

like.

[0090]

Compound (XXXVI) with m = 2 or 3 can be produced by isomerizing compound (XXXV) with acids, in the same manner as in the production of compound (XVI) from compound (XV) mentioned hereinabove. Preferred examples of the acid catalyst to be used include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid, phosphoric acid, etc.; organic acids such as acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid, 10-camphorsulfonic acid, etc.; boron trifluoride-ether complex, etc. The acid catalyst is used in an amount of approximately from 0.01 to 10 mols, preferably approximately from 0.01 to 5.0 mols per mol of compound (XXXV). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; sulfoxides such as dimethylsulfoxide, etc.; water, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 10 minutes to 12 hours, preferably from 10 minutes to 2 hours. The reaction temperature is generally from -10 to 200°C, preferably from -10 to 100°C. The product (XXXVI) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired,

however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0091]

Compound (XXXVI) with m = 1 can be produced by treating compound (XXXII) with trimethylsilylcyanide in the presence of a Lewis acid, then treating the resulting intermediate with an acid to remove its trimethylsilyloxy group and thereafter reducing it at its cyano group, in the same manner as in the production of compound (XVI) from compound (X) mentioned hereinabove. The Lewis acid includes, for example, zinc iodide, anhydrous aluminium chloride, anhydrous zinc chloride, anhydrous iron chloride, etc. The Lewis acid catalyst is used in an amount of approximately from 0.01 to 10 mols, preferably approximately from 0.01 to 1.0 mol per mol of compound (XXXII). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 10 minutes to 12 hours, preferably from 30 minutes to 3 hours. The reaction temperature is generally from -10 to 200°C, preferably from -10 to 100°C. The intermediate can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified

through means of separation, such as, through recrystallization, distillation, chromatography or the like. Next, the intermediate is treated with an acid. Preferably, the acid includes, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid, phosphoric acid, etc.; organic acids such as acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid, 10-camphorsulfonic acid, etc.; boron trifluoride-ether complex, etc. The acid is used in an amount of approximately from 1 to 100 mols, preferably approximately from 1 to 10 mols per mol of compound (XXXII). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; sulfoxides such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 30 minutes to 12 hours, preferably from 30 minutes to 5 hours. The reaction temperature is generally from 0 to 200°C, preferably from 20 to 150°C. The reduction of the cyano group in the resulting intermediate can be conducted under the same conditions as those for the production of compound (XV) from compound (XII). The product (XXXVI) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily

purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0092]

Compound (I) can also be produced by reacting compound (XXXVI) with a carboxylic acid or with its salt or reactive derivative. The carboxylic acid includes, for example, compounds of the formula R^1-COOH (where R^1 is as defined above). The reactive derivatives of the carboxylic acid include, for example, acid halides (e.g., acid chlorides, acid bromides, etc.), acid amides (e.g., acid amides with pyrazole, imidazole, benzotriazole, etc.), mixed acid anhydrides (e.g., mixed mono-C_{1-4} alkyl carbonate anhydrides derived from monomethyl carbonate, monoethyl carbonate, monoisopropyl carbonate, mono-tert-butyl carbonate; mixed mono-C_{7-10} aralkyl carbonate anhydrides derived from monobenzyl carbonate, mono(p-nitrobenzyl) carbonate, monoallyl carbonate; mixed C_{1-6} aliphatic carboxylic acid anhydrides derived from acetic acid, cyanoacetic acid, propionic acid, butyric acid, isobutyric acid, valeric acid, isovaleric acid, pivalic acid, trifluoroacetic acid, trichloroacetic acid, acetacetic acid; mixed C_{7-11} aromatic carboxylic acid anhydrides derived from benzoic acid, p-toluic acid, p-chlorobenzoic acid; mixed organic sulfonic acid anhydrides derived from methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.), acid azides, active esters (e.g., diethoxyphosphates, diphenoxyphosphates, p-nitrophenyl esters, 2,4-dinitrophenyl esters, cyanomethyl esters, pentachlorophenyl esters, esters with N-hydroxysuccinimide, esters with N-hydroxyphthalimide, esters with 1-hydroxybenzotriazole, esters with 6-chloro-1-hydroxybenzotriazole, esters with 1-hydroxy-1H-2-pyridone, etc.), active thioesters

(e.g., 2-pyridyl thioesters, 2-benzothiazolyl thioesters, etc.), etc.

[0093]

In place of using the reactive derivative, the carboxylic acid or its salt may be directly reacted with compound (XXXVI) in the presence of a suitable condensing agent. The condensing agent includes, for example, N,N'-di-substituted carbodiimides such as N,N'-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (WSC) hydrochloride, etc.; azolides such as N,N'-carbonyldiimidazole, etc.; dehydrating agents such as N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, phosphorus oxychloride, alkoxyacetylenes, etc.; 2-halogenopyridinium salts such as 2-chloromethylpyridinium iodide, 2-fluoro-1-methylpyridinium iodide, etc. It is believed that the reaction with the condensing agent may advance via the reactive derivative of the carboxylic acid used. The carboxylic acid of the formula R^1-COOH (where R^1 is as defined above) or its reactive derivative is used generally at approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 2.0 mols per mol of compound (XXXVI). The reaction is advantageously conducted in a solvent inert to the reaction. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. Where acid halides are used

as the reactive derivatives of carboxylic acids, the reaction may be conducted in the presence of a de-acidifying agent in order to remove the released hydrogen halide from the reaction system. The de-acidifying agent includes, for example, inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc. It is desirable that such a de-acidifying agent is previously added to the reaction system. The reaction time varies, depending on the reagents and the solvents used, and is generally from 30 minutes to 24 hours, preferably from 30 minutes to 4 hours. The reaction temperature is generally from 0 to 100°C, preferably from 0 to 70°C.

[0094]

Compound (I) can also be produced by adding to compound (XXXV) a carboxylic acid of the formula R^1-COOH (where R^1 is as defined above) or its reactive derivative, stirring them under acidic conditions for from 5 minutes to 3 hours, preferably from 10 minutes to 1 hour, at from 0 to 100°C, preferably from 0 to 70°C, and thereafter adding a de-acidifying agent such as that mentioned above to the reaction system to thereby make the resulting intermediate acylated. The process is accompanied by isomerization of the reaction system to give compound (I). The carboxylic acid or its reactive derivative is used generally at approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 2.0 mols per mol of compound (XXXV). The reaction is advantageously conducted in a solvent inert to the reaction. The solvent is not

specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. The product (I) thus obtained can be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0095]

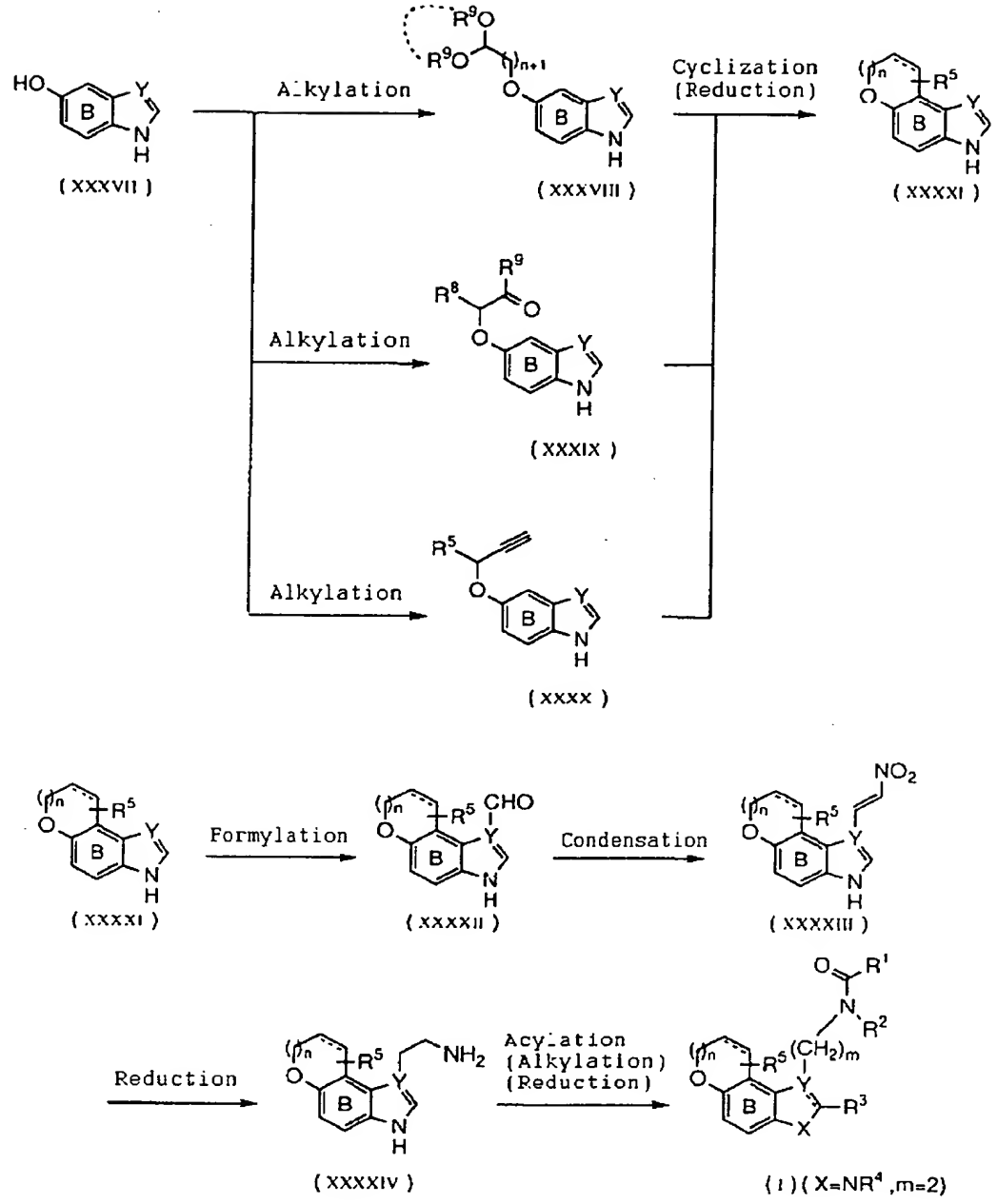
To obtain compound (I) wherein R^2 is an alkyl group, the acylated compound as obtained in the above is alkylated with a corresponding alkylating agent (e.g., alkyl halides, sulfonates with alcohols) in the presence of a base. The alkylating agent is used in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 2.0 mols per mol of compound (I) to be alkylated therewith. The base includes, for example, inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide,

etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 2.0 mols per mol of compound (I). The reaction is advantageously conducted in a solvent inert to the reaction. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 30 minutes to 48 hours, preferably from 30 minutes to 6 hours. The reaction temperature is generally from -20 to 200°C, preferably from -10 to 150°C. The product (I) can be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

To obtain compound (I) where the double-bond moiety has been reduced, the double-bond moiety in compound (I) is catalytically reduced under the same conditions as those for the production of compound (VII) from compound (VIII).

[0097]

Reaction Process 4:



[0098]

Compound (XXXVII) can be produced using <u>per se</u> known methods, for example, using the methods described in J. Chem. Soc., p. 2525 (1952); ibid., p. 1165 (1954); J. Org. Chem. Vol. 49, p. 4833 (1984); J. Heterocyclic Chem., Vol. 24, p. 941 (1987); J. Med. Chem., Vol. 17, p. 747 (1974); Helv. Chim. Acta, Vol.

48, p. 252 (1965), or methods analogous thereto.
[0099]

Compound (XXXVIII) can be produced by reacting compound (XXXVII) with a corresponding alkylating agent (e.g., alkyl halides, sulfonates with alcohols) in the presence of a base. The alkylating agent is used in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 2.0 mols per mol of compound (XXXVII) to be alkylated therewith. The base includes, for example, inorganic bases such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 2.0 mols per mol of compound (XXXVII). The reaction is advantageously conducted in a solvent inert to the reaction. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane,

etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 30 minutes to 48 hours, preferably from 1 to 24 hours. The reaction temperature is generally from -20 to 200°C, preferably from 0 to 150°C. The product (XXXVIII) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0100]

Compound (XXXIX) can be produced by reacting compound (XXXVII) with a corresponding α-haloketone in the presence of a base. The α-haloketone is used in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 2.0 mols per mol of compound (XXXVII). The base includes, for example, inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 2.0 mols per mol of compound

(XXXVII). The reaction is advantageously conducted in a solvent inert to the reaction. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; ketones such as acetone, methyl ethyl ketone, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 30 minutes to 48 hours, preferably from 1 to 24 hours. The reaction temperature is generally from -20 to 200°C, preferably from 0 to 150°C. The product (XXXIX) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0101]

Compound (XXXX) can be produced by reacting compound (XXXVII) with a corresponding alkylating agent (e.g., substituted acetylene-alkyl halides, sulfonates with substituted acetylene alcohols, etc.) in the presence of a base. The alkylating agent is used in an amount of approximately from 1.0 to 20.0 mols, preferably approximately from 1.0 to 10.0 mols per mol of compound (XXXVII). The base includes, for example, inorganic bases such as sodium carbonate, potassium

carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 2.0 mols per mol of compound (XXXVII). The reaction is advantageously conducted in a solvent inert to the reaction. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 30 minutes to 48 hours, preferably from 1 to 24 hours. The reaction temperature is generally from -20 to 200°C, preferably from 0 to 150°C. The product (XXXX) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified

through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0102]

If the alkylation is not selectively directed towards the hydroxyl group of the compound, the amino group of the compound shall be protected and de-protected, if necessary. The protection and the de-protection of the amino group may be conducted in accordance with conventional known methods. For example, referred to is the disclosure in the chapter "Protection for the Amino Group" in "Protecting Groups in Organic Synthesis" by T. W. Green (2nd Ed., 1991).

[0103]

Compound (XXXXI) can be produced by per se known cyclization of compound (XXXVIII), (XXXIX) or (XXXX). For example, the cyclization can be conducted by a method of heating the compound, or a method of treating the compound with an acidic substance, or a method of treating the compound with a basic substance, or methods analogous thereto.

The cyclization under heat is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, high-boiling-point hydrocarbons such as 1,2,3,4-tetrahydronaphthalene, bromobenzene, etc.; high-boiling-point ethers such as diphenyl ether, diethyleneglycol dimethyl ether, etc.; N,N-dimethylaniline, N,N-diethylaniline, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 10 minutes to 24 hours, preferably from 10 minutes to 10 hours. The reaction temperature is generally from 100 to 300°C, preferably from 100 to 250°C.

[0104]

The acidic substance for the cyclization includes, for example, phosphorus oxychloride, phosphorus pentachloride, phosphorus pentoxide, phosphorus trioxide, thionyl chloride, hydrochloric acid, hydrochloric acid, sulfuric acid, phosphoric acid, polyphosphoric acid, p-toluenesulfonic acid, etc. The acidic substance is used in an amount of approximately from 0.5 to 100 mols, preferably approximately from 5.0 to 20 mols per mol of compound (XXXVIII), (XXXIX) or (XXXX). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, aromatic hydrocarbons such as benzene, toluene, etc.; saturated hydrocarbons such as cyclohexane, hexane, etc.; ethers such as tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; acid anhydrides such as acetic anhydride, etc.; sulfoxides, such as dimethylsulfoxide, etc.; water, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 30 minutes to 12 hours, preferably from 30 minutes to 6 hours. The reaction temperature is generally from 0 to 200°C, preferably from 0 to 150°C.

[0105]

The basic substance for the cyclization includes, for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, etc. The basic substance is used in an amount of approximately from 0.5 to 100 mols, preferably approximately from 5.0 to 20 mols per mol of

compound (XXXVIII), (XXXIX) or (XXXX). The reaction is advantageously conducted in either the absence of a solvent or the presence of a solvent inert to the reaction. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; ketones such as acetone, methyl ethyl ketone, etc.; water, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 30 minutes to 12 hours, preferably from 30 minutes to 6 hours. The reaction temperature is generally from 0 to 200°C, preferably from 0 to 150°C.

The double-bond moiety in the ring as newly formed by the cyclization may optionally be reduced in the same manner as in the production of compound (VII) from compound (VIII).

The product (XXXXI) obtained through the cyclization can be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0106]

Compound (XXXXII) can be produced from compound (XXXXI) using per se known methods, for example, using the methods described in The Chemistry of Heterocyclic Compounds, Vol. 25, Part 3 (W. J. Houlihan, ed., John Wiley and Sons, Inc., New York), p. 361 (1979); J. Chem. Soc., p. 3842 (1954); Tetrahedron, Vol. 36, p. 2505 (1980); Monatsh. Chem., Vol. 117, p. 375 (1986), or methods analogous thereto.

[0107]

Compound (XXXXIII) can be produced from compound (XXXXII) and nitromethane through aldol condensation in the presence of a base. This is obtained as a single

E-form or Z-form configurational isomer or as a mixture of such E- and Z-isomers. Nitromethane is used in an amount of approximately from 1.0 to 100 mols, preferably approximately from 1.0 to 50 mols per mol of compound (XXXXII). The base includes, for example, inorganic bases such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, etc.; primary amines such as methylamine, propylamine, butylamine, benzylamine, aniline, etc.; ammonium acetate, alumina, etc. The base is used in an amount of approximately from 0.01 to 5.0 mols, preferably from 0.1 to 1.0 mol per mol of compound (XXXXII). The reaction is advantageously conducted in a solvent inert thereto. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol, propanol, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; water, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 30 minutes to 72 hours, preferably from 30 minutes to 24 hours. The reaction temperature is generally from -20 to 200°C, preferably from -10 to 150°C. The product (XXXXIII) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0108]

Compound (XXXXIV) can be produced by reducing compound (XXXXIII). The reducing agent usable for this includes, for example, metal hydrides such as aluminium

hydride, diisobutyl aluminium hydride, etc.; metal hydride complexes such as lithium aluminium hydride, sodium borohydride, lithium borohydride, sodium borohydride cyanide, etc. As the hydrogenation catalyst, for example, usable are Raney nickel, platinum oxide, platinum on activated carbon palladium on activated carbon, palladium on barium sulfate nickel, copper-chromium oxide, rhodium, cobalt, ruthenium, etc. Additives (promoters) that enhance the activity of a catalyst used can be added to the reaction system. Acidic additives advantageously usable for this purpose include, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, perchloric acid, hydrobromic acid, phosphoric acid, etc.; organic acids such as acetic acid, trifluoroacetic acid, oxalic acid, phthalic acid, fumaric acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, p-toluenesulfonic acid, 10-camphorsulfonic acid, etc. Basic additives are also advantageously usable and include, for example, sodium hydroxide, potassium hydroxide, etc. Regarding the amount of the reducing agent to be used, the metal hydride is used in an amount of approximately from 1.0 to 10 mols, preferably approximately from 1.0 to 3.0 mols per mol of compound (42) while the metal hydride complex is used in an amount of approximately from 1.0 to 10 mols, preferably from 1.0 to 3.0 mols per mol of compound (XXXXIII). For the hydrogenation, a catalyst such as Raney nickel, Raney cobalt or the like is used in an amount of approximately from 10 to 1000% by weight, preferably approximately from 100 to 300% by weight relative to compound (XXXXIII). The reaction is advantageously conducted in a solvent inert thereto. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol,

ethanol, propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; organic acids such as formic acid, acetic acid, etc. Mixed solvents comprising them are also preferably used. The reaction time varies, depending on the activity of the catalyst and the amount thereof used, and is generally from 1 hour to 100 hours, preferably from 1 hour to 50 hours. The reaction temperature is generally from 0 to 120°C, preferably from 20 to 80°C. Where Raney nickel or the like catalyst is used, the hydrogen pressure shall be generally from 1 to 100 atmospheres. The product (XXXXIV) can be used in the next reaction step, while it is in the reaction mixture or in the form of a crude product. If desired, however, it may be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

[0109]

Compound (XXXXIV) can also be produced using per se known methods, for example, using the methods described in J. Med. Chem., Vol. 35, p. 3625 (1992); Tetrahedron, Vol. 48, p. 1039 (1992), or methods analogous thereto.

[0110]

Compound (I) can be produced by reacting compound (XXXXIV) with a carboxylic acid or with its salt or reactive derivative. The carboxylic acid includes, for example, compounds of the formula, R^1-COOH (where R^1 is as defined above). The reactive derivatives of the carboxylic acid include, for example, acid halides (e.g., acid chlorides, acid bromides, etc.), acid amides (e.g., acid amides with pyrazole, imidazole,

benzotriazole, etc.), mixed acid anhydrides (e.g., mixed mono-C_{1-4} alkyl carbonate anhydrides derived from monomethyl carbonate, monoethyl carbonate, monoisopropyl carbonate, mono-tert-butyl carbonate; mixed mono-C_{7-10} aralkyl carbonate anhydrides derived from monobenzyl carbonate, mono(p-nitrobenzyl) carbonate, monoallyl carbonate; mixed C_{1-6} aliphatic carboxylic acid anhydrides derived from acetic acid, cyanoacetic acid, propionic acid, butyric acid, isobutyric acid, valeric acid, isovaleric acid, pivalic acid, trifluoroacetic acid, trichloroacetic acid, acetacetic acid; mixed C_{7-11} aromatic carboxylic acid anhydrides derived from benzoic acid, p-toluic acid, p-chlorobenzoic acid; mixed organic sulfonic acid anhydrides derived from methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.), acid azides, active esters (e.g., diethoxyphosphates, diphenoxyphosphates, p-nitrophenyl esters, 2,4-dinitrophenyl esters, cyanomethyl esters, pentachlorophenyl esters, esters with N-hydroxysuccinimide, esters with N-hydroxyphthalimide, esters with 1-hydroxybenzotriazole, esters with 6-chloro-1-hydroxybenzotriazole, esters with 1-hydroxy-1H-2-pyridone, etc.), active thioesters (e.g., 2-pyridyl thioesters, 2-benzothiazolyl thioesters, etc.), etc.

[0111]

In place of using the reactive derivative, the carboxylic acid or its salt may be directly reacted with compound (XXXXIV) in the presence of a suitable condensing agent. The condensing agent includes, for example, N,N'-di-substituted carbodiimides such as N,N'-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (WSC) hydrochloride, etc.; azolides such as N,N'-carbonyldiimidazole, etc.; dehydrating agents such as N-ethoxycarbonyl-2-ethoxy-

1,2-dihydroquinoline, phosphorus oxychloride, alkoxyacetylenes, etc.; 2-halogenopyridinium salts such as 2-chloromethylpyridinium iodide, 2-fluoro-1-methylpyridinium iodide, etc. It is believed that the reaction with the condensing agent may advance via the reactive derivative of the carboxylic acid used. The carboxylic acid of the formula R^1-COOH (where R1 is as defined above) or its reactive derivative is used generally in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 2.0 mols per mol of compound (XXXXIV). The reaction is advantageously conducted in a solvent inert to the reaction. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. In the case that acid halides are used as the reactive derivatives of carboxylic acids, the reaction may be conducted in the presence of a de-acidifying agent in order to remove the released hydrogen halide from the reaction system. The de-acidifying agent includes, for example, inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-

methylmorpholine, etc. It is desirable that such a de-acidifying agent is previously added to the reaction system. The reaction time varies, depending on the reagents and the solvents used, and is generally from 30 minutes to 24 hours, preferably from 30 minutes to 4 hours. The reaction temperature is generally from 0 to 100°C, preferably from 0 to 70°C.

[0112]

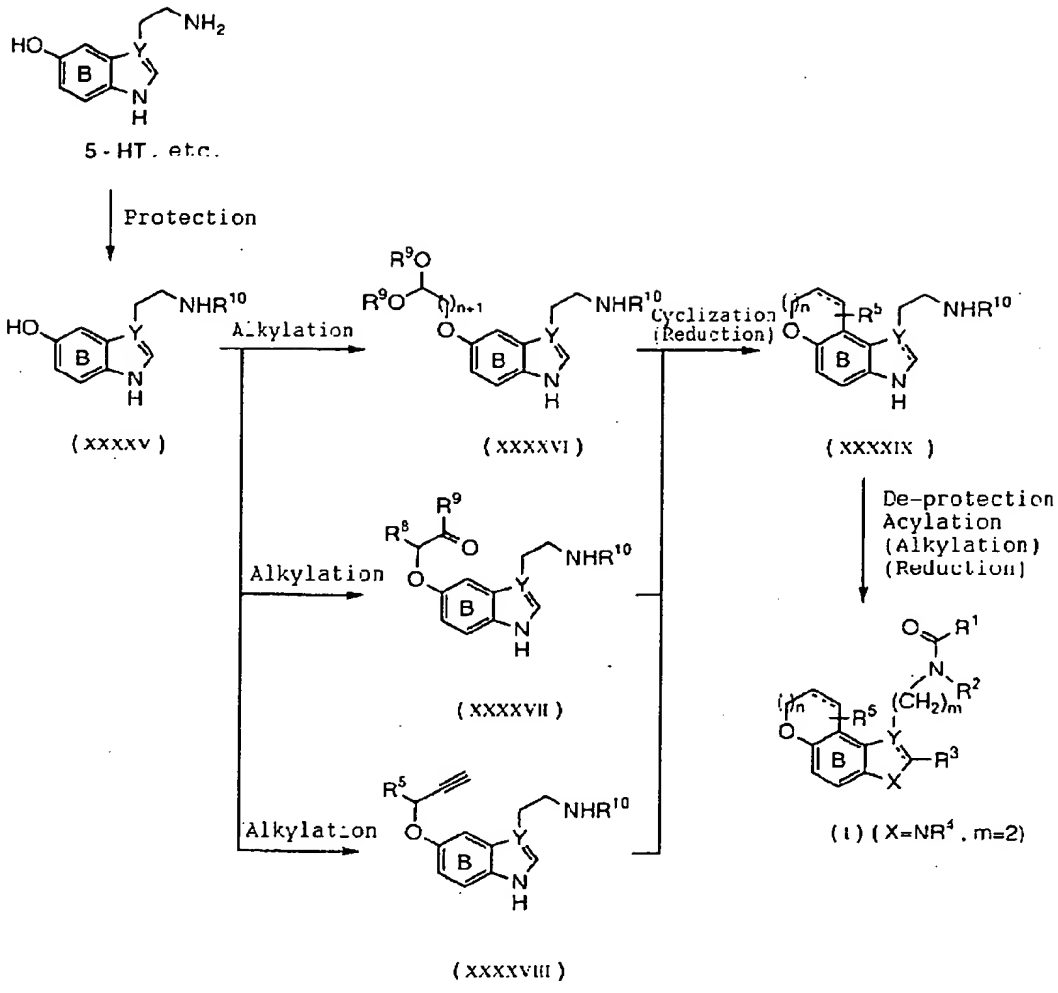
To obtain compound (I) wherein R^2 is an alkyl group, the acylated compound as obtained in the above is alkylated with a corresponding alkylating agent (e.g., alkyl halides, sulfonates with alcohols) in the presence of a base. The alkylating agent is used in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 2.0 mols per mol of compound (I) to be alkylated therewith. The base includes, for example, inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, etc.; aromatic amines such as pyridine, lutidine, etc.; tertiary amines such as triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, etc.; alkali metal hydrides such as sodium hydride, potassium hydride, etc.; metal amides such as sodium amide, lithium diisopropylamide, lithium hexamethyldisilazide, etc.; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc. The base is used in an amount of approximately from 1.0 to 5.0 mols, preferably approximately from 1.0 to 2.0 mols per mol of compound (I). The reaction is advantageously conducted in a solvent inert to the reaction. The solvent is not specifically defined, so far as the reaction advances therein. Preferably, it includes, for example, alcohols such as methanol, ethanol,

propanol, etc.; ethers such as diethyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, etc.; hydrocarbons such as benzene, toluene, cyclohexane, hexane, etc.; amides such as N,N-dimethylformamide, N,N-dimethylacetamide, etc.; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, etc.; nitriles such as acetonitrile, propionitrile, etc.; sulfoxides such as dimethylsulfoxide, etc. Mixed solvents comprising them are also preferably used. The reaction time is generally from 30 minutes to 48 hours, preferably from 30 minutes to 6 hours. The reaction temperature is generally from -20 to 200°C, preferably from -10 to 150°C. The product (I) can be isolated from the reaction mixture by ordinary methods, and it can be easily purified through means of separation, such as, through recrystallization, distillation, chromatography or the like.

Compound (I) where the double-bond moiety has been reduced can be produced in the same manner as in the production of compound (VII) from compound (VIII).

[0113]

Reaction Process 5:



[0114]

Compound (XXXXV) can be produced, for example, by protecting the primary amino group of 5-hydroxytryptamine (5-HT). The protection of the amino group may be conducted using ordinary known methods. For example, referred to is the disclosure in the chapter "Protection for the Amino group" in "Protecting Groups in Organic Synthesis" by T. W. green (2nd Ed., 1991).

Compound (XXXXVI) can be produced from compound (XXXXV) in the same manner as in the production of compound (XXXVIII) from compound (XXXVII).

Compound (XXXXVII) can be produced from compound (XXXXV) in the same manner as in the production of compound (XXXIX) from compound (XXXVII).

Compound (XXXXVIII) can be produced from compound (XXXXV) in the same manner as in the production of compound (XXXX) from compound (XXXVII).

Compound (XXXXIX) can be produced from compound (XXXXVI), (XXXXVII) or (XXXXVIII) in the same manner as in the production of compound (XXXXI) from compound (XXXVIII), (XXXIX) or (XXXX). It can also be produced using per se known methods, for example, using the methods described in Tetrahedron Lett., Vol. 36, p. 7019 (1995) or methods analogous thereto. Compound (XXXXIX) where the double-bond moiety has been reduced can be produced in the same manner as in the production of compound (VII) from compound (VIII).

[0115]

Compound (I) can be produced by de-protecting the protected, amino side group in compound (XXXXIX) followed by processing the resulting compound in the same manner as in the production of compound (I) from compound (XXXXIV). The de-protection of the amino group may be conducted in accordance with the conventional by known methods. For example, referred to is the disclosure in chapter "Protection for the Amino Group" in "Protecting Groups in Organic Synthesis" by T. W. Green (2nd Ed., 1991).

[0116]

Just after their isomerization, the configurational isomers (E- and Z forms) of the above-mentioned compounds (XII), (XV), (XXXIV) or (XXXV) can be isolated and purified through ordinary means of separation, for example, through extraction, recrystallization, distillation, chromatography or the like to obtain pure compounds. If desired, the isomerization of the double-bond moiety in these

compounds may be conducted, for example, under heat or through treatment with acid catalysts, transition metal catalysts, metal catalysts, radical catalysts or strong base catalysts or even through light irradiation to obtain the corresponding pure isomers, by means of the methods described in "Shin Jikken Kagaku Koza (New Lectures on Experimental Chemistry)" Vol. 14 (edited by Japan Chemical Society), pp. 251-253; "Jikken Kagaku Koza (Lectures on Experimental Chemistry 19)", 4th Ed., pp. 273-274 (edited by the Japan Chemical Society), or methods analogous thereto.

Compound (I) includes stereoisomers, depending on the substituents therein. The present invention encompasses not only single isomers but also mixtures of these.

If desired, any of the above-mentioned reaction steps may be accompanied by known de-protection, acylation, alkylation, hydrogenation, oxidation, reduction, carbon-chain extension and substituent-exchange reaction, either singly or in a combination of two or more of such reactions, to obtain compound (I). For these reactions, for example, referred to are the methods described in "Shin Jikken Kagaku Koza (New lectures on Experimental Chemistry)", Vols. 14 and 15 (edited by Japan Chemical Society, published in 1977, 1978), etc, or methods analogous thereto.

[0117]

In the above-mentioned reaction steps for producing the compounds of the present invention and those for producing the starting compounds for the compounds of the invention, where the starting compounds for these have, as substituents, an amino group, carboxyl group and/or hydroxyl group, these groups may be protected by ordinary protective groups such as those generally employed in peptide chemistry. After the reaction, the protective groups may be

removed to obtain the intended products.

The amino-protective group includes, for example, formyl group, C_{1-6} alkylcarbonyl groups (e.g., acetyl, ethylcarbonyl, etc.), C_{1-6} alkyloxycarbonyl groups (e.g., methoxycarbonyl, ethoxycarbonyl, etc.), benzoyl group, C_{7-10} aralkylcarbonyl groups (e.g., benzylcarbonyl, etc.), trityl group, phthaloyl group, N,N-dimethylaminomethylene group, etc. These protective groups may optionally be substituted by one to three substituents halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.), a nitro group, etc.

The carboxyl-protective group includes, for example, C_{1-6} alkyl groups (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), phenyl group, trityl group, silyl group, etc. These protective groups may optionally be substituted by one to three substituents halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.), formyl group, C_{1-6} alkylcarbonyl groups (e.g., acetyl propionyl, butylcarbonyl, etc.), nitro group, etc.

The hydroxyl protective group includes, for example, C_{1-6} alkyl groups (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), phenyl group, C_{7-10} aralkyl groups (e.g., benzyl, etc.), C_{1-6} alkylcarbonyl groups (e.g., acetyl, propionyl, etc.), benzoyl group, C_{7-10} aralkylcarbonyl groups (e.g., benzylcarbonyl, etc.), tetrahydropyranyl group, tetrahydrofuranyl group, silyl group, etc. These protective groups may optionally be substituted by one to three substituents halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.), C_{1-6} alkyl groups (e.g., methyl, ethyl, propyl, etc.), phenyl group, C_{7-10} aralkyl groups (e.g., benzyl, etc.), nitro group, etc.

These protective groups may be removed using <u>per se</u> known methods or in accordance with them. For

example, employable are methods using acids, bases, reducing means, ultraviolet rays, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium acetate, etc.
[0118]

The compound (I) of the present invention can be isolated and purified through known means, such as, through solvent extraction, liquid conversion, solvent transfer, crystallization, recrystallization, chromatography, etc. The intermediates and their salts for the compound (I) of the invention can also be isolated and purified using known methods such as those mentioned above but, as the case may be, they can be directly used in the next reaction step without being isolated.

Where the compound (I) is purified through recrystallization, for example, employable are water, alcohols (e.g., methanol, ethanol, n-propanol, isopropanol, etc.), aromatic hydrocarbons (e.g., benzene, toluene, xylene, etc.), halogenated hydrocarbons (e.g., dichloromethane, chloroform, etc.), saturated hydrocarbons (e.g., hexane, heptane, cyclohexane, etc.), ethers (e.g., diethyl ether, isopropyl ether, tetrahydrofuran, dioxane, etc.), ketones (e.g., acetone, methyl ethyl ketone, etc.), nitriles (e.g., acetonitrile, etc.), sulfoxides (e.g., dimethylsulfoxide, etc.), acid amides (e.g., N,N-dimethylformamide, etc.), esters (e.g., ethyl acetate, etc.), carboxylic acids (e.g., acetic acid, propionic acid, etc.), etc. These can be used singly or, if desired, as mixtures comprising two or more at suitable ratios, for example, at from 1/1 to 1/10.

Where the products are obtained as free compounds in the above-mentioned reaction steps, they can be converted into their salts by ordinary methods. Where they are obtained as salts, the salts can be converted

into free compounds or other salts by ordinary methods. The compound (I) thus obtained can be isolated and purified from the reaction mixtures by known means, for example, through solvent transfer, concentration, solvent extraction, fractionating distillation, crystallization, recrystallization, chromatography, etc.

Where the compound (I) exists as configurational isomers, diastereomers, conformers, etc., it can be isolated separately, if desired, in accordance with the above-mentioned means of separation and purification. Mixtures of optically-active compound (I) can be isolated into d-forms and l-forms by means of ordinary optical resolution.

[0119]

The compound (I) of the present invention shows a high binding affinity for melatonin receptors and is highly selective especially in ML-1 receptors. The compound has low toxicity, while having few side effects, and is therefore useful in medicines.

The compound (I) of the present invention acts as melatonin agonist or antagonist in mammals (e.g., mouse, rat, hamster, rabbit, feline, canine, bovine, sheep, monkey, human, etc.) and is useful in composition with a binding affinity for melatonin receptor, especially in a composition agonistic towards melatonin receptor or a composition antagonistic towards melatonin receptor, and, therefore, it can be used for preventing and curing biorhythmic control disorders and various other disorders that may be affected by melatonin, for example, sleep-awake rhythm disorders, jet-lag, shift-work syndrome, seasonal melancholia, genital and neuroendocrine disorders, senile dementia, Alzheimer's disease, various disorders accompanied by aging (e.g., for preventing aging, etc.), cerebrovascular disorders, stress, epilepsy,

convulsions, anxiety, depression, Parkinsonism, hypertension, glaucoma, cancer, insomnia, diabetes, etc. In addition, it is also effective for immunoregulation, nootropic, tranquilization and ovulatory regulation (e.g., contraception). The compound (I) of the present invention can be used, for example, in biorhythm regulators, preferably medicines for sleep disorder (e.g., sleep-inducing medicines, etc.), sleep-awake rhythm regulators (including those for controlling sleep-awake rhythm), medicines for physilogical syndromes caused by time-zone changes, for example, so-called jet-lag, etc.

[0120]

The compound (I) of the present invention has low toxicity and can be administered safely through peroral or parenteral routes (e.g., for local administration, rectal administration, intravenous administration, etc.), either directly or as pharmaceutical compositions to be mixed with pharmaceutically acceptable carriers by using per se known methods, for example, as tablets (including sugar-coated tablets, film-coated tablets), powders, granules, capsules (including soft capsules), liquids, injections, suppositories, sustained release preparations, plasters and also as chewing gum, etc. The amount of compound (I) is in the composition of the present invention is approximately from 0.01 to 100% by weight of the total weight of the composition. The dose of the composition varies, depending on the subject to which the composition is administered, the administration route, the disorder, etc. For example, when the composition is administered to an adult patient suffering from sleep disorders, it is preferable to administer once daily or severally divided dosages in an amount of approximately from 0.1 to 20 mg/kg body weight, preferably approximately from 0.2 to 10 mg/kg body

weight, more preferably approximately from 0.5 to 10 mg/kg body weight, in terms of the amount of the active ingredient, compound (I). The composition may be used with other active ingredients (e.g., benzodiazepine-type medicines comprising benzodiazepine compounds such as triazolam, diazepam, alprazolam, estazolam, etc.; requlating agents of sleep rhythm comprising fatty acid derivatives such as butoctamide and its salt, etc.; sleep ruducing substances comprising cis-9,10-octadecenamide, etc.) Such other active ingredient and the compound (I) may be mixed by means of per se known methods to give pharmaceutical compositions (e.g., tablets, powders, granules, capsules including soft capsules, liquids, injections, suppositories, sustained release preparations, etc.); or they are separately formulated into different preparations, which may be administered to one and the same subject either simultaneously or at different times.

[0121]

Pharmaceutically acceptable carriers employable in the production of the composition of the present invention include various organic and inorganic carrier substances which are known to be usable in pharmaceutical compositions. For example, they include excipients, lubricants, binders, disintegrants, etc. in solid compositions; solvents, solubilizers, suspending agents, isotonizing agents, buffers, pain-easing agents, etc. in liquid compositions. If desired, ordinary preservatives, antioxidants, colorants, sweeteners, adsorbents, moisturizers, and other additives may also be employed.

Excipients employable in the present invention include, for example, lactose, white sugar, D-mannitol, starch, corn starch, crystalline cellulose, light silicic acid anhydride, etc.

Lubricants include, for example, magnesium

stearate, calcium stearate, talc, colloidal silica, etc.

Binders include, for example, crystalline cellulose, white sugar, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinyl pyrrolidone, starch, sucrose, gelatin, methyl cellulose, sodium carboxymethyl cellulose, etc.

Disintegrants include, for example, starch, carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium cross-carmellose, sodium carboxymethyl starch, L-hydroxypropyl cellulose, etc.

Solvents include, for example, water for injection, alcohol, propyleneglycol, macrogol, sesame oil, corn oil, olive oil, etc.

Solubilizers include, for example, polyethyleneglycol, propyleneglycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, etc.

Suspending agents include, for example, surfactants such as stearyl triethanolamine, sodium laurylsulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzetonium chloride, glycerin monostearate, etc.; hydrophilic polymers such as polyvinyl alcohol, polyvinyl pyrrolidone, sodium carboxymethyl cellulose, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, etc.

Isotonizing agents include, for example, glucose, D-sorbitol, sodium chloride, glycerin, D-mannitol, etc.

Buffers include, for example, buffer liquids such as phosphates, acetates, carbonates, citrates, etc.

Pain-easing agents include, for example, benzyl alcohol, etc.

Preservatives include, for example, parahydroxybenzoates, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid,

etc.

Antioxidants include, for example, sulfites, ascorbic acid, α-tocopherol, etc.

[0123]

[DESCRIPTION OF PREFERRED EMBODIMENTS OF THE INVENTION]

The present invention is described in detail by means of the following reference examples, examples and experimental examples, which, however, serve merely to illustrate the embodiments of the invention but not to restrict the invention. Various modifications and changes can be made in the present invention without departing from the spirit and scope of the invention.

"Room temperature" as referred to in the following reference examples and examples generally indicates a temperature of from 10°C to 35°C. Unless otherwise specifically indicated, "%" is percent by weight.

The abbreviations referred to herein are defined as follows:

s : singlet
d : doublet
t : triplet
q : quartet
m : multiplet
br: broad
J : coupling constant
Hz: hertz
$CDCl_3$: deuterochloroform
DMSO-d_6 : (dimethylsulfoxide)-d_6
NMR : proton nuclear magnetic resonance

[0124]

[Examples]

Reference Example 1

2,3-Dihydrobenzofuran-5-carbaldehyde

Titanium chloride (28 ml) was dropwise added to a dichloromethane (100 ml) solution containing 2,3-dihydrobenzofuran (10.0g, 83.2 mmols) and

dichloromethyl methyl ether (11.3 ml, 0.125 mmols), while cooling with ice. The mixture was stirred for 1 hour, while still cooling with ice, and then water was added thereto. Dichloromethane was removed under reduced pressure, and the residue was extracted with ethyl acetate. The extract was washed with a saturated saline solution, then dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified through silica-gel chromatography (hexane/ethyl acetate = 1/1) to obtain 11.4g (yield: 92%) of the target compound. This was oily.

NMR ($CDCl_3$) δ: 3.28 (2H, t, J = 8.8 Hz), 4.70 (2H, t, J = 8.8 Hz), 6.88 (1H, d, J = 8.4 Hz), 7.67 (1H, dd, J = 1.0 Hz, 8.4 Hz), 7.75 (1H, d, J = 1.0 Hz), 9.83 (1H, s)

[0125]

Reference Example 2

Ethyl (E)-3-(2,3-dihydrobenzofuran-5-yl)-2-propenoate

60% sodium hydride (3.39g, 84.6 mmols) was added to a tetrahydrofuran (150 ml) solution of triethyl phosphonoacetate (19.0g, 84.6 mmols) while cooling with ice, and the mixture was stirred for 20 minutes. To this was dropwise added a tetrahydrofuran (15 ml) solution of 2,3-dihydrobenzofuran-5-carbaldehyde (11.4g, 76.9 mmols) and stirred further for 1 hour. Water was added to the reaction mixture, which was then extracted with ethyl acetate. The extract was washed with a saturated saline solution, then dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified through silica-gel column chromatography (hexane/ethyl acetate = from 95/5 to 9/1) to obtain 14.7g (yield: 88%) of the target compound. This was oily.

NMR ($CDCl_3$) δ: 1.33 (3H, t, J = 7.2 Hz), 3.23 (2H, t, J = 8.8 Hz), 4.25 (2H, q, J = 7.2 Hz), 4.63 (

2H, t, J = 8.8 Hz), 6.28 (1H, d, J = 16.0 Hz), 6.79 (1H, d, J = 8.4 Hz), 7.31 (1H, d, J = 8.4 Hz), 7.41 (1H, s), 7.64 (1H, d, J = 16.0 Hz)

[0126]

Reference Example 3

Ethyl 3-(2,3-Dihydrobenzofuran-5-yl)propionate

5% Palladium-carbon (1g, containing 50% water) was added to an ethanol (150 ml) solution of ethyl (E)-3-(2.3-dihydrobenzofuran-5-yl)-2-propenoate (14.7g, 66.7 mmols), and the mixture was stirred in a hydrogen atmosphere at room temperature for 2 hours. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to obtain 14.6g (yield: 99%) of the target compound. This was oily.

NMR ($CDCl_3$) δ: 1.24 (3H, t, J = 7.2 Hz), 2.57 (2H, t, J = 7.8 Hz), 2.88 (2H, t, J = 7.8 Hz), 3.18 (2H, t, J = 8.6 Hz), 4.13 (2H, q, J = 7.2 Hz), 4.55 (2H, t, J = 8.6 Hz), 6.70 (1H, d, J = 8.2 Hz), 6.94 (1H, d, J = 8.2 Hz), 7.05 (1H, s)

The compound obtained herein was used in the next reaction without being further purified.

Reference Example 4

Ethyl 3-(7-Bromo-2,3-dihydrobenzofuran-5-yl)propionate

Bromine (10.5g, 65.8 mmols) was dropwise added to an acetic acid (150 ml) solution containing ethyl 3-(2,3-dihydrobenzofuran-5-yl)propionate (14.5g, 65.8 mmols) and sodium acetate (5.94g, 72.4 mmols), and the mixture was stirred at room temperature for 1 hour. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. Water was added to the residue, which was then extracted with ethyl acetate. The extract was washed with a saturated saline solution and then dried with anhydrous magnesium sulfate. This was concentrated under reduced pressure to obtain 19.2g (yield: 97%) of the target compound.

This was oily.

NMR ($CDCl_3$) δ: 1.25 (3H, t, J = 7.2 Hz), 2.57 (2H, t, J = 7.6 Hz), 2.85 (2H, t, J = 7.6 Hz), 3.28 (2H, t, J = 8.8 Hz), 4.13 (2H, q, J = 7.2 Hz), 4.65 (2H, t, J = 8.8 Hz), 6.97 (1H, s), 7.11 (1H, s)

The compound obtained herein was used in the next reaction without being further purified.

Reference Example 5

3-(7-Bromo-2,3-dihydrobenzofuran-5-yl)propionic Acid

An aqueous solution (100 ml) of sodium hydroxide (15g) was added to a tetrahydrofuran (20 ml) solution of ethyl 3-(7-bromo-2,3-dihydrobenzofuran-5-yl)propionate (19.1g, 63.8 mmols), and the mixture was stirred at room temperature for 3 hours. The reaction mixture was made acidic with hydrochloric acid added thereto, and this was then extracted with ethyl acetate. The extract was washed with a saturated saline solution, then dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate/hexane to obtain 12.8g (yield: 73%) of the target compound.

m.p.: 117-118°C

NMR ($CDCl_3$) δ: 2.64 (2H, t, J = 7.4 Hz), 2.87 (2H, t, J = 7.4 Hz), 3.82 (2H, t, J = 8.8 Hz), 4.65 (2H, t, J = 8.8 Hz), 6.97 (1H, s), 7.11 (1H, s)

[0129]

Reference Example 6

4-Bromo-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one

Thionyl chloride (10.1 ml, 0.139 mols) was added to 3-(7-bromo-2,3-dihydrobenzofuran-5-yl)propionic acid (12.7g, 46.2 mmols), the mixture was stirred at 75°C for 30 minutes, and the reaction mixture was then concentrated under reduced pressure to obtain an acid

chloride. The thus-prepared acid chloride was dropwise added to a 1,2-dichloroethane (100 ml) suspension of anhydrous aluminium chloride (6.77g, 50.8 mmols) while cooling with ice, and the mixture was stirred for 30 minutes. The reaction mixture was poured into water and then extracted with ethyl acetate. The extract was washed with a saturated saline solution, then dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified through silica-gel column chromatography (hexane/ethyl acetate = 8.2) and then recrystallized from ethyl acetate/isopropyl ether to obtain 1.00g (yield: 9%) of the target compound.

m.p.: 149-150°C

NMR ($CDCl_3$) δ: 2.64-2.72 (2H, m), 3.08 (2H, t, J = 5.8 Hz), 3.57 (2H, t, J = 9.0 Hz), 4.76 (2H, t, J = 9.0 Hz), 7.41-7.43 (1H, m)

[0130]

Reference Example 7

(E)-(4-bromo-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-ylidene)acetonitrile

60% Sodium hydride (0.17g, 4.35 mmols) was added to a tetrahydrofuran (20 ml) solution of diethyl cyanomethylphosphonate (0.77g, 4.35 mmols) while cooling with ice, and the mixture was stirred for 20 minutes. To this was added a tetrahydrofuran (10 ml) solution of 4-bromo-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one (1.00g, 3.95 mmols), and the mixture was stirred at room temperature further for 2 hours. Water was added to the reaction mixture, which was then extracted with ethyl acetate. The extract was washed with a saturated saline solution, then dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified through silica-gel column chromatography (hexane/ethyl acetate = from 85/15 to 8/2) and then recrystallized from ethyl

acetate/isopropyl ether to obtain 0.47g (yield: 43%) of the target compound.

m.p.: 200-203°C

NMR ($CDCl_3$) δ: 3.02-3.18 (4H, m), 3.41 (2H, t, J = 8.8 Hz), 4.77 (2H, t, J = 8.8 Hz), 5.42-5.46 (1H, m), 7.31 (1H, s)

[0131]

Reference Example 8

2-(1,6,7,8-Tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethylamine hydrobromide.

Raney nickel (0.4g, W2) and 4 M ammonia/ethanol solution (10 ml) were added to an ethanol (30 ml) suspension of (E)-(4-bromo-1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-ylidene)acetonitrile (0.44g, 1.59 mmols) and stirred in a hydrogen atmosphere (at from 4 to 5 atmospheres) at room temperature for 5 hours. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethanol (50 ml), and 5% palladium-carbon (1g, containing 50% water) was added thereto and stirred in a hydrogen atmosphere (at ordinary pressure) at room temperature for 4 hours. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to obtain 0.42g (yield: 93%) of the target compound. This was amorphous.

NMR ($CDCl_3$) δ: 1.58-1.83 (2H, m), 1.97-2.36 (2H, m), 2.70-2.96 (6H, m), 3.03-3.36 (3H, m), 4.42-4.64 (2H, m), 6.61 (1H, d, J = 8.2 Hz), 6.95 (1H, d, J = 8.2 Hz)

[0132]

Reference Example 9

3-(3-Fluoro-4-methoxyphenyl)propionic acid

Malonic acid (7.5g, 72.1 mmols) and piperidine (0.84g, 9.83 mmols) were added to a pyridine (20 ml) solution of 3-fluoro-4-methoxybenzaldehyde (10.1g, 65.5 mmols), and the mixture was stirred under heat at 120°C

for 7 hours. The reaction mixture was poured into water containing ice, and the powder that precipitated was taken out through filtration. The powder was dried and dissolved in acetic acid (300 ml) without being further purified. To this was added 5% palladium-carbon (3g, containing 50% water), and the mixture was stirred in a hydrogen atmosphere at room temperature for 2 hours. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to obtain 8.54g (yield: 66%) of the target compound.

m.p.: 114-117°C

NMR ($CDCl_3$) δ: 2.65 (2H, t, J = 7.5 Hz), 2.89 (2H, t, J = 7.5 Hz), 3.87 (3H, s), 6.80-7.00 (3H, m)

[0133]

Reference Example 10

5-Fluoro-6-methoxy-1-indanone

In the same manner as in Reference Example 6, the target compound was obtained from 3-(3-fluoro-4-methoxyphenyl)propionic acid. The yield was 91%.

m.p.: 152-153°C (recrystallized from methanol/ethyl acetate)

NMR ($CDCl_3$) δ: 2.71 (2H, t, J = 5.7 Hz), 3.08 (2H, t, J = 5.7 Hz), 3.92 (3H, s), 7.17 (1H, d, J = 10.3 Hz), 7.29 (d, J = 8.1 Hz)

Elemental Analysis for $C_{10}H_9FO_2$:

Calcd.: C 66.66; H 5.03

Found: C 66.82; H 5.06

[0134]

Reference Example 11

(E)-(5-Fluoro-6-methoxyindan-1-ylidene) acetonitrile

In the same manner as in Reference Example 7, the target compound was obtained from 5-fluoro-6-methoxy-1-indanone and diethyl cyanomethylphosphonate. The yield was 75%.

m.p.: 197-199°C (recrystallized from hexane/ethyl

acetate)

NMR ($CDCl_3$) δ: 3.00-3.19 (4H, m), 3.92 (3H, s), 5.53 (1H, t, J = 2.2 Hz), 7.02 (1H, d, J = 7.6 Hz), 7.07 (1H, d, J = 10.3 Hz)

Elemental Analysis for $C_{12}H_{10}FNO$:

Calcd.: C 70.93; H 4.96; N 6.89

Found: C 70.65; H 5.13; N 6.99

[0135]

Reference Example 12

2-(5-Fluoro-6-methoxyindan-1-yl)ethylamine

In the same manner as in Reference Example 8, the target compound was obtained from (E)-(5-fluoro-6-methoxyindan-1-ylidene)acetonitrile. The yield was 88%. The compound was oily.

NMR ($CDCl_3$) δ: 1.50-1.80 (2H, m), 1.90-2.08 (1H, m), 2.20-2.40 (1H, m), 2.67-2.90 (4H, m), 3.00-3.20 (1H, m), 3.87 (3H, s), 6.80 (1H, d, J = 8.1 Hz), 6.92 (1H, d, J = 11.0 Hz)

[0136]

Reference Example 13

N-[2-(5-fluoro-6-methoxyindan-1-yl)ethyl] propionamide

Propionyl chloride (2.5g, 27.0 mmols) was gradually and dropwise added to a tetrahydrofuran (20 ml) solution containing 2-(5-fluoro-6-methoxyindan-1-yl)ethylamine (4.35g, 20.8 mmols) and triethylamine (4.21g, 41.6 mmols) while cooling with ice. After having been stirred at room temperature for 2 hours, the reaction mixture was poured into water, and the organic substance was extracted out with ethyl acetate. The extract was washed with a saturated saline solution and water and then dried with anhydrous magnesium sulfate, and the solvent was removed through distillation under reduced pressure. The resulting residue was purified through silica-gel column chromatography (ethyl acetate/hexane = 90/10) to obtain

4.87g (yield: 88%) of the target compound.

m.p.: 76-78°C

NMR ($CDCl_3$) δ: 1.16 (3H, t, J = 7.7 Hz), 1.47-1.81 (2H, m), 1.94-2.41 (2H, m), 2.21 (2H, q, J = 7.7 Hz), 2.70-2.90 (2H, m), 3.00-3.20 (1H, m), 3.38 (2H, q, J = 7.3 Hz), 3.87 (3H, s), 5.50 (1H, br s), 6.82 (1H, d, J= 8.1 Hz), 6.92 (1H, d, J = 11.4 Hz)

Elemental Analysis for $C_{15}H_{20}NFO_2$:

Calcd.: C 67.90; H 7.60; N 5.28

Found: C 67.83; H 7.27; N 5.25

[0137]

Reference Example 14

N-[2-(5-fluoro-6-hydroxyindan-1-yl)ethyl] propionamide

Boron tribromide (7.9g, 31.5 mmols) was gradually and dropwise added to a dichloromethane (100 ml) solution of N-[2-(5-fluoro-6-methoxyindan-1-yl)ethyl]propionamide (4.18g, 15.8 mmols) while cooling with ice. After having been stirred for 2 hours while still cooling with ice, the reaction mixture was poured into water containing ice and then stirred at room temperature for 3 hours, and the organic substance was extracted with ethyl acetate. The extract was washed with a saturated saline solution and water and then dried with anhydrous magnesium sulfate, and the solvent was removed through distillation under reduced pressure. The resulting residue was purified through silica-gel column chromatography (ethyl acetate/hexane = 9/1) to obtain 3.68g (yield: 93%) of the target compound.

m.p.: 93-96°C (recrystallized from ethyl acetate/hexane)

NMR ($CDCl_3$) δ: 1.20 (3H, t, J = 7.7 Hz), 1.47-1.80 (2H, m), 1.88-2.10 (1H, m), 2.22 (2H, q, J = 7.7 Hz), 2.20-2.40 (1H, m), 2.65-2.90 (2H, m), 2.95-

3.13 (1H, m), 3.37 (2H, q, J = 7.5 Hz), 5.59 (1H, brs), 6.09 (1H, brs), 6.83 (1H, d, J = 8.4 Hz), 6.89 (1H, d, J = 10.6 Hz)

Elemental Analysis for $C_{14}H_{18}NFO_2$:

Calcd.: C 66.91; H 7.22; N 5.57

Found: C 66.84; H 7.10; N 5.54

[0138]

Reference Example 15

N-[2-(5-fluoro-6-(2-propynyloxy)indan-1-yl)ethyl] propionamide

Potassium carbonate (1.37g, 9.95 mmols) and propargyl bromide (2.4g, 19.9 mmols) were added to a dimethylformamide (10 ml) solution of N-[2-(5-fluoro-6-hydroxyindan-1-yl)ethyl]propionamide (0.5g, 1.99 mmols) and stirred at 120°C for 2 hours. The reaction solution was poured into water, and the organic substance was extracted out with ethyl acetate. The extract was washed with a saturated saline solution and water and then dried with anhydrous magnesium sulfate, and the solvent was removed through distillation under reduced pressure. The resulting residue was purified through silica-gel column chromatography (ethyl acetate) to obtain 0.56g (yield: 97%) of the target compound.

m.p.: 78-81°C (recrystallized from ethyl acetate)

NMR ($CDCl_3$) δ: 1.16 (3H, t, J = 7.5 Hz), 1.50-1.83 (2H, m), 1.91-2.11 (1H, m), 2.21 (2H, q, J = 7.5 Hz), 2.20-2.41 (1H, m), 2.55 (1H, t, J = 2.3 Hz), 2.65-2.95 (2H, m), 3.00-3.20 (1H, m), 3.38 (2H, q, J = 7.5 Hz), 4.74 (2H, d, J = 2.2 Hz), 5.47 (1H, br s), 6.91 (1H, s), 6.96 (1H, s)

[0139]

Example 1

N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]acetamide

Aqueous 1 N sodium hydroxide solution (1.5 ml) and

acetic anhydride (0.050 ml, 0.528 mmols) were added to a tetrahydrofuran (1.5 ml) solution of 2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethylamine hydrobromide (0.10g, 0.352 mmols), and the mixture was stirred at room temperature for 30 minutes. Water was added to the reaction mixture, which was then extracted with ethyl acetate. The extract was washed with a saturated saline solution, then dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from isopropyl ether/hexane to obtain 0.057g (yield: 66%) of the target compound.

m.p.: 78-79°C

NMR ($CDCl_3$) δ: 1.53-2.12 (3H, m), 1.96 (3H, s),2.20-2.38 (1H, m),2.70-2.96 (2H, m),3.02-3.40 (5H, m), 4.45-4.68 (2H, m), 5.46 (1H, br s), 6.62 (1H, d, J = 8.0 Hz), 6.96 (1H, d, J = 8.0 Hz)

Elemental Analysis for $C_{15}H_{19}NO_2$:

Calcd.: C 73.44; H 7.81; N 5.71

Found: C 73.55; H 7.90; N 5.60

[0140]

Example 2

N-[2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide

In the same manner as in Example 1, the target compound was obtained from 2-(1,6,7,8-tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethylamine hydrobromide and propionyl chloride. The yield was 78%.

m.p.: 102-104°C (recrystallized from isopropyl ether/hexane)

NMR ($CDCl_3$) δ: 1.14 (3H, t, J = 7.6 Hz), 1.55-2.38 (4H, m), 2.18 (2H, q, J = 7.6 Hz), 2.69-2.99 (2H, m), 3.02-3.40 (5H, m), 4.42-4.63 (2H, m), 5.61 (1H, br s), 6.62 (1H, d, J = 7.8 Hz), 6.95 (1H, d, J = 7.8 Hz)

Elemental Analysis for $C_{16}H_{21}NO_2$:

Calcd.: C 74.10; H 8.16; N 5.40
Found: C 74.20; H 8.37; N 5.25

[0141]

Example 3

N-[2-(3,7,8,9-tetrahydropyrano[3,2-e]indol-1-yl)ethyl]acetamide

In the same manner as in Example 1, the target compound was obtained from 2-(3,7,8,9-tetrahydropyrano[3,2-e]indol-1-yl)ethylamine and acetic anhydride. The yield was 54%.

m.p.: 185-186°C (recrystallized from methanol/isopropyl ether)

NMR ($CDCl_3$) δ: 1.96 (3H, s), 2.03-2.15 (2H, m), 3.09 (2H, t, J = 6.8 Hz), 3.20 (2H, t, J = 6.8 Hz), 3.56 (2H, q, J = 6.4 Hz), 4.18 (2H, t, J = 7.0 Hz), 5.60 (1H, brs), 6.73 (1H, d, J = 8.8 Hz), 6.96 (1H, d, J = 2.2 Hz), 7.09 (1H, d, J = 8.8 Hz), 7.98 (1H, brs)

Elemental Analysis for $C_{15}H_{18}N_2O_2$:

Calcd.: C 69.74; H 7.02; N 10.84
Found: C 69.69; H 7.09; N 10.79

[0142]

Example 4

N-[2-(3,7,8,9-tetrahydropyrano[3,2-e]indol-1-yl)ethyl]propionamide

In the same manner as in Example 1, the target compound was obtained from 2-(3,7,8,9-tetrahydropyrano[3,2-e]indol-1-yl)ethylamine and propionyl chloride. The yield was 67%.

m.p.: 147-148°C (recrystallized from methanol/isopropyl ether)

NMR ($CDCl_3$) δ: 1.14 (3H, t, J = 7.6 Hz), 2.02-2.16 (2H, m), 2.17 (2H, q, J = 7.6 Hz), 3.08 (2H, t, J = 7.0 Hz), 3.19 (2H, t, J = 7.0 Hz), 3.57 (2H, q, J = 6.2 Hz), 4.18 (2H, t, J = 5.0 Hz), 5.60 (1H, br s), 6.72 (1H, d, J = 8.4 Hz), 6.94 (1H, d, J =

2.2 Hz), 7.09 (1H, d, J = 8.4 Hz), 8.11 (1H, br s)

Elemental Analysis for $C_{16}H_{20}N_2O_2$:

Calcd.: C 70.56; H 7.40; N 10.29

Found: C 70.69; H 7.54; N 10.27

[0143]

Example 5

N-[2-(3,7,8,9-tetrahydropyrano[3,2-e]indol-1-yl)ethyl]butyramide

In the same manner as in Example 1, the target compound was obtained from 2-(3,7,8,9-tetrahydropyrano[3,2-e]indol-1-yl)ethylamine and butyryl chloride. The yield was 62%.

m.p.: 154-155°C (recrystallized from methanol/isopropyl ether)

NMR ($CDCl_3$) δ: 0.93 (3H, t, J = 7.2 Hz), 1.57-1.73 (2H, m), 2.06-2.16 (4H, m), 3.08 (2H, t, J = 6.8 Hz), 3.19 (2H, t, J = 6.4 Hz), 3.52-3.63 (2H, m), 4.18 (2H, t, J = 5.2 Hz), 5.58 (1H, br s), 6.72 (1H, d, J = 8.4 Hz), 6.94 (1H, d, J = 2.6 Hz), 7.09 (1H, d, J = 8.4 Hz), 8.05 (1H, br s)

Elemental Analysis for $C_{17}H_{22}N_2O_2$:

Calcd.: C 71.30; H 7.74; N 9.78

Found: C 71.45; H 7.86; N 9.78

[0144]

Example 6:

N-[2-(1,2,3,7,8,9-hexahydropyrano[3,2-e]indol-1-yl)ethyl]acetamide

Platinum oxide (45 mg) and hydrochloric acid (2 ml) were added to an ethanol (40 ml) solution of N-[2-3,7,8,9-tetrahydropyrano[3,2-e]indol-1-yl)ethyl]acetamide (0.90g, 3.48 mmols), and the mixture was stirred in a hydrogen atmosphere (at from 4 to 5 atmospheres) at 50°C for 6 hours. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was neutralized with a saturated, aqueous sodium hydrogencarbonate solution,

then saturated with salt and extracted with ethyl acetate. The extract was washed with a saturated saline solution, then dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate/isopropyl ether to obtain 0.53g (yield: 59%) of the target compound.

m.p.: 137-138°C

NMR ($CDCl_3$) δ: 1.78-2.05 (4H, m), 1.90 (3H, s), 2.68 (2H, t, J = 6.6 Hz), 2.96-3.14 (1H, m), 3.31-3.50 (3H, m), 3.65 (1H, t, J = 9.4 Hz), 3.98-4.10 (1H, m), 4.15-4.26 (1H, m), 6.13 (1H, br s), 6.49 (1H, d, J = 8.4 Hz), 6.57 (1H, d, J = 8.4 Hz)

Elemental Analysis for $C_{15}H_{20}N_2O_2$:

Calcd.: C 69.20; H 7.74; N 10.76

Found: C 69.65; H 7.74; N 10.61

[0145]

Example 7:

N-[2-(1,2,3,7,8,9-hexahydropyrano[3,2-e]indol-1-yl)ethyl]propionamide

In the same manner as in Example 6, the target compound was obtained from N-[2-(3,7,8,9-tetrahydropyrano[3,2-e]indol-1-yl)ethyl]propionamide. The yield was 42%.

m.p.: 106-107°C (recrystallized from ethyl acetate/isopropyl ether)

NMR ($CDCl_3$) δ: 1.11 (3H, t, J = 7.6 Hz), 1.76-2.08 (4H, m), 2.13 (2H, q, J = 7.6 Hz), 2.68 (2H, t, J = 6.4 Hz), 2.99-3.16 (1H, m), 3.31-3.51 (3H, m), 3.65 (1H, t, J =9.4 Hz), 3.98-4.10 (1H, m), 4.15-4.24 (1H, m), 6.10 (1H, br s), 6.48 (1H, d, J = 8.4 Hz), 6.56 (1H, d, J = 8.4 Hz)

Elemental Analysis for $C_{16}H_{22}N_2O_2$:

Calcd.: C 70.04; H 8.08; N 10.21

Found: C 70.18; H 8.34; N 10.13

[0146]

Example 8

N-[2-(1,2,3,7,8,9-hexahydropyrano[3,2-e]indol-1-yl)ethyl]butyramide

In the same manner as in Example 6, the target compound was obtained from N-[2-(3,7,8,9-tetrahydropyrano[3,2-e]indol-1-yl)ethyl]butyramide. The yield was 55%.

m.p.: 91-93°C (recrystallized from ethyl acetate/isopropyl ether)

NMR ($CDCl_3$) δ: 0.92 (3H, t, J = 7.2 Hz), 1.53-1.71 (2H, m), 1.76-1.88 (2H, m), 1.91-2.10 (2H, m), 2.05 (2H, q, J = 8.2 Hz), 2.68 (2H, t, J = 6.6 Hz), 2.99-3.16 (1H, m), 3.30-3.50 (3H, m), 3.64 (1H, t, J = 9.2 Hz), 3.98-4.09 (1H, m), 4.15-4.23 (1H, m), 6.11 (1H, br s), 6.48 (1H, d, J = 8.4 Hz), 6.56 (1H, d, J= 8.4 Hz)

Elemental Analysis for $C_{17}H_{24}N_2O_2$:

Calcd.: C 70.80; H 8.39; N 9.71

Found: C 70.55; H 8.45; N 9.68

[0147]

Example 9

N-[2-(5-fluoro-3,7,8,9-cyclopenta[f][1]benzopyran-9-yl)ethy l]propionamide

A bromobenzene (15 ml) solution of N-[2-(5-fluoro-6-(2-propionyloxy)indan-1-yl)ethyl]propionamide (0.55g, 1.90 mmols) was stirred at 250°C in a sealed tube for 8 hours. The reaction mixture was cooled, and then the solvent was removed through distillation under reduced pressure. The resulting residue was purified through silica-gel column chromatography (ethyl acetate) to obtain 0.27g (yield: 49%) of the target compound.

m.p.: 108-110°C (recrystallized from ethyl acetate/hexane)

NMR ($CDCl_3$) δ: 1.14 (3H, t, J = 7.5 Hz), 1.50-1.81 (2H, m), 1.89-2.30 (2H, m), 2.18 (2H, q, J = 7.5 Hz), 2.55-3.00 (2H, m), 3.16-3.40 (3H, m), 4.66-

4.92 (2H, m), 5.40 (1H, br s), 5.88 (1H, dt, J = 9.9 Hz, 3.7 Hz), 6.43-6.53 (1H, m), 6.80 (1H, d, J = 10.6 Hz)

[0148]

Example 10

N-[2-(5-fluoro-1,2,3,7,8,9-hexahydrocyclopenta[f][1] benzopyran-9-yl)ethyl]propionamide

In the same manner as in Reference Example 3, the target compound was obtained from N-[2-(5-fluoro-3,7,8,9-cyclopenta[f][1]benzopyran-9-yl)ethyl]propionamide. The yield was 80%.

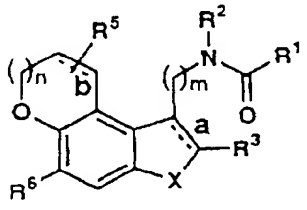
m.p.: 106-108°C (recrystallized from ethyl acetate/hexane)

NMR ($CDCl_3$) δ: 1.14 (3H, t, J = 7.7 Hz), 1.47-1.84 (2H, m), 1.84-2.27 (4H, m), 2.17 (2H, q, J = 7.7 Hz), 2.60-3.01 (4H, m), 3.05-3.20 (1H, m), 3.21-3.41 (2H, m), 4.05-4.20 (1H, m), 4.27-4.39 (1H, m), 5.40 (1H, br s), 6.77 (1H, d, J = 10.6 Hz)

[0149]

The chemical structures of the compounds obtained in Examples 1 to 10 are shown in Table 1 below.

Table 1



Example No.	R^1	R^2	R^3	R^5	R^6	X	m	n	a	b
1	Me	H	H	H	H	CH_2	2	0	—	—
2	Et	H	H	H	H	CH_2	2	0	—	—
3	Me	H	H	H	H	NH	2	1	=	—
6	Et	H	H	H	H	NH	2	1	=	—
6	Pr	H	H	H	H	NH	2	1	=	—
6	Me	H	H	H	H	NH	2	1	—	—
7	Et	H	H	H	H	NH	2	1	—	—
6	Pr	H	H	H	H	NH	2	1	—	—
9	Pr	H	H	H	F	CH_2	2	1	—	=
10	Pr	H	H	H	F	CH_2	2	1	—	—

[0150]

Formulation Example 1

(1) Compound obtained in Example 1 10.0g
(2) Lactose 60.0g
(3) Corn starch 35.0g
(4) gelatin 3.0g
(5) Magnesium stearate 2.0g

A mixture comprised of 10.0g of the compound obtained in Example 1, 60.0g of lactose and 35.0g of corn starch was granulated with 30 ml of aqueous 10 wt.% gelatin solution (3.0g as gelatin) by sieving through a 1 mm-mesh sieve, then dried and again sieved. The resulting granules were mixed with 2.0g of magnesium stearate and then formed into tablets. The resulting core tablets were coated with a sugar coating of an aqueous suspension comprising sucrose, titanium dioxide, talc and arabic gum. The thus-coated tablets were glazed with bees wax. Thus, obtained were 1000 sugar-coated tablets.

[0151]

Formulation Example 2

(1) Compound obtained in Example 1 10.0g

(2) Lactose	70.0g
(3) Corn starch	50.0g
(4) Soluble starch	7.0g
(5) Magnesium stearate	3.0g

10.0g of the compound obtained in Example 1 and 3.0g of magnesium stearate were granulated with 70 ml of an aqueous solution of soluble starch (7.0g as soluble starch), then dried and mixed with 70.0g of lactose and 50.0g of corn starch. The mixture formed into 1000 tablets.

[0152]

Experimental Example 1

Inhibition of 2-[^{125}I]iodomelatonin binding activity

The forebrains of 7-day-old chicken (white leghorn) were homogenized with ice-cold assay buffer (50 mM Tris-HCl, pH 7.7 at 25°C) and centrifuged at 44,000 x g for 10 minutes at 4°C. The pellet was washed once with the same buffer and storred at -30°C until use. For the assay, the frozen tissue pellet was thawed and homogenized with the assay buffer to make a protein concentration of 0.3 - 0.4 mg/ml. An 0.4 ml aliquot of this homogenate was incubated with a test compound and 80 pM 2-[^{125}I]iodomelatonin in a total volume of 0.5 ml for 90 minutes at 25°C. The reaction was terminated by adding 3 ml of ice-cold assay buffer immediately followed by vaccum filtration on Whatman GF/B which was further washed twice with 3 ml of ice-cold assay buffer. The radioactivity on the filter was determined by means of γ-counter. Specific binding was calculated by subtracting non-specific binding which was determined in the presence of 10^{-5}M melatonin. The 50% inhibiting concentration (IC_{50}) was determined by the log-probit analysis.

[0153]

Table 2

Action of inhibiting 2-[^{125}I]iodomelatonin binding

Compounds of Example	IC_{50} (nM)
1	0.28
2	0.13
3	0.46
4	0.13
5	0.082
7	0.46
8	0.22
Melatonin	0.68

From the results in Table 2 above, it is understood that the compound (I) of the present invention has excellent melatonin receptor-agonistic activity.

[0154]

[EFFECTS OF THE INVENTION]

As has been described in detail and demonstrated concretely, the compounds (I) or its their salts of the present invention has excellent affinity for melatonin receptors. Therefore, the present invention provides medicines which are clinically useful for preventing and curing various disorders associated with melatonin activity *in vivo*. In addition, the compound (I) or its salts of the present invention has excellent *in vivo* behavior and have excellent solubility in water.

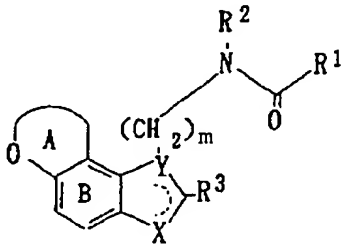
[NAME OF DOCUMENT] ABSTRACT OF THE DISCLOSURE

[ABSTRACT]

[PROBLEM] Provision of medicines which are clinically useful for preventing and curing various disorders associated with melatonin activity

[METHODS FOR SOLVING THE PROBLEM]

A compound of the formula



(I)

wherein R^1 is an optionally substituted hydrocarbon group, an optionally substituted amino group, or an optionally-substituted heterocyclic group; R^2 is a hydrogen atom, or an optionally substituted hydrocarbon group; R^3 is a hydrogen atom, an optionally substituted hydrocarbon group, or an optionally-substituted heterocyclic group; X is CHR^4, NR^4, O or S (R^4 is a hydrogen atom or an optionally substituted hydrocarbon group); Y is C, CH or N, provided that when X is CH_2, Y is C or CH; ----- is a single bond or a double bond; ring A is an optionallysubstituted, 5- to 7-membered oxygen-containing heterocyclic ring; ring B is an optionally substituted benzene ring; and m is an integer of 1 to 4, or a salt thereof.

[SELECTED FIGURE] None